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PICTORIAL REVIEW

# The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney complex): imaging findings with clinical and pathological correlation

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**Abstract** The complex of myxomas, spotty skin pigmentation and endocrine overactivity, or Carney complex (CNC), is a familial multiple endocrine neoplasia and lentiginosis syndrome. CNC is inherited in an autosomal dominant manner and is genetically heterogeneous. Its features overlap those of McCune-Albright syndrome and other multiple endocrine neoplasia (MEN) syndromes. Spotty skin pigmentation is the major clinical manifestation of the syndrome, followed by multicentric heart myxomas, which occur at a young age and are the lethal component of the disease. Myxomas may also occur on the skin (eyelid, external ear canal and nipple) and the breast. Breast myxomas, when present, are multiple and bilateral among female CNC patients, an entity which is also described as "breast-myxomatosis" and is a characteristic feature of the syndrome. Affected CNC patients often have tumours of two or more endocrine glands, including primary pigmented nodular adrenocortical disease (PPNAD), an adrenocorticotropin hormone (ACTH)-independent cause of Cushing's syndrome, growth hormone (GH)-secreting and prolactin (PRL)-secreting pituitary adenomas, thyroid adenomas or carcinomas, testicular neoplasms (large-cell calcifying Sertoli cell tumours [LCCSCT]) and ovarian lesions (cysts and cancinomas). Additional infrequent but characteristic manifestations of CNC are psammomatous melanotic schwannomas (PMS), breast ductal adenomas (DAs) with tubular features, and osteochondromyxomas or "Carney bone tumour".

*Teaching Points*

- *Almost 60 % of the known CNC kindreds have a germline inactivating mutations in the PRKAR1A gene.*
- *Spotty skin pigmentation is the major clinical manifestation of CNC, followed by heart myxomas.*
- *Indicative imaging signs of PPNAD are contour abnormality and hypodense spots within the gland.*
- *Two breast tumours may present in CNC: myxoid fibroadenomas (breast myxomatosis) and ductal adenomas.*
- *Additional findings of CNC are psammomatous melanotic schwannomas (PMSs) and osteochondromyxomas.*

**Keywords** Carney complex · Protein kinase A · Spotty skin pigmentation · Myxoma · Primary pigmented nodular adrenocortical disease · Large-cell calcifying sertoli cell tumour · Psammomatous melanotic schwannoma · Ductal adenoma · Osteochondromyxoma

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## Introduction

The complex of myxomas, spotty skin pigmentation and endocrine overactivity, or Carney complex (CNC) (MIM No. 160980), is a familial lentiginosis and multiple endocrine

neoplasia syndrome described in 1985 by Carney [1, 2]. More than 500 patients with CNC have been reported since then, worldwide, and the majority of them (almost 70 %) presented with positive family history [3, 4]. The median age at detection is 20 years, but the initial presentation varies among patients. Life expectancy of patients with CNC is decreased mainly due to heart-related causes, which account for 57 % of deaths of CNC patients [5]. Noteworthy, CNC is different from Carney triad. Although the two conditions share part of their names, Carney triad presents with gastrointestinal stromal tumours (GISTs), lung chondromas, paragangliomas, adrenal adenomas and pheochromocytomas, oesophageal leiomyomas and other hamartomatous lesions.

## Molecular genetics and penetrance of CNC

Linkage analysis studies have identified two CNC genetic loci: (1) a 6.4-cM region on chromosome 2 (2p16) and (2) a 17-cM region on chromosome 17 (17q22-24) [6, 7]. Almost 60 % of the known CNC kindreds have a germline inactivating mutation in the *PRKAR1A* gene, which codes for the regulatory subunit type 1α (RIa) of the cAMP-dependent protein kinase A (PKA), located on chromosome 17q23-24 [4, 8]. Inactivating mutations of the *PRKAR1A* gene lead to aberrant function of PKA and increased phosphorylation of targets implicated in cell transcription, metabolism, cell cycle progression and apoptosis [9]. The *PRKAR1A* gene seemingly functions as a tumour suppressor gene in tumours of CNC patients [10, 11]. The penetrance for CNC due to *PRKAR1A* defects is close to 100 % by the age of 50, but this does not apply to kindreds with CNC caused by other genetic defects [5, 12]. Although CNC has a similar presentation as other lentiginosis syndromes, like Peutz-Jeghers syndrome, Cowden disease and Bannayan-Zonana syndrome, studies have failed to demonstrate any correlation of their genetic basis [13–18].

## Diagnosis of CNC

The diagnostic criteria for CNC are included in Table 1, as established by Stratakis et al. [5]. The diagnosis of CNC is established when a patient exhibits either: (1) two of the manifestations of the disease listed in the Table 1 or (2) one of these manifestations and one of the supplemental criteria (an affected first-degree relative or an inactivating mutation of the *PRKAR1A* gene). Differential diagnosis includes syndromes that present with multiple endocrine neoplasias, like MEN syndromes (thyroid, pituitary and adrenal involvement), or with similar manifestations from skin, bones and other tissues, like Peutz-Jeghers syndrome (lentigines), McCune-Albright syndrome (cafe-au-lait spots, bone tumours, pituitary and adrenal involvement) and others.

## Skin lesions

Skin abnormalities are present in almost 77 % of the CNC patients [5]. The most common skin lesions are spotty skin pigmentations (lentigines), epithelioid blue-nevi and skin myxomas. Rare skin manifestations include: ephelides (hyperpigmentation of the basal epidermal unit), junctional nevi (nodular accumulation of melanocytes in the dermis-epidermis junction), café-au-lait spots and atypical blue or compound nevi. Many patients present with a combination of the aforementioned skin lesions.

### Spotty skin pigmentations

#### *Clinical features*

Spotty skin pigmentations are the most common clinical manifestation among CNC patients. The number of pigmented lesions ranges from few to myriad [1, 5, 10]. The pigmentations are small (up to 2 mm in diameter), brown, dark brown or black, round or irregularly shaped, slightly elevated or non-elevated, and they are suggestive of lentigines. Lentigines are usually seen on the face (at the periocular and perioral zones, including the vermilion border of the lips), the eyelids and the conjunctiva of the sclera, the trunk, and the hands and fingers (Fig. 1). They have also been observed on the feet, the vulva, the anal verge and the glans penis. They usually assume their final appearance during adolescence and, unlike the most common age-related lesions, they start to discolour after the 4th decade of life.

#### *Pathological features*

Lentigines are characterised by hyperpigmentation of the basal epidermal layer with hyperplasia of melanocytes and increased melanin in melanocytes and basal keratinocytes, with or without elongation of the rete ridges.

### Epithelioid blue-nevi

#### *Clinical features*

These spotty skin pigmentations are bigger (up to 8 mm in diameter), blue to black domed lesions (Fig. 2). Although their presentation is similar to malignant melanoma, these tumours usually have a benign progress in CNC patients.

**Table 1** Diagnostic criteria for CNC (from [5] with written permission)

| Diagnostic criteria for CNC | |
|---|---|
| • Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa) | |
| • Myxoma (cutaneous and mucosal)[a] | |
| • Cardiac myxoma[a] | |
| • Breast myxomatosis[a] or fat-suppressed MRI findings suggestive of this diagnosis | |
| • PPNAD[a] or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test | |
| • Acromegaly due to GH-producing adenoma[a] | |
| • LCCSCT[a] or characteristic calcification on testicular ultrasonography | |
| • Thyroid carcinoma (at any age)[a] or multiple, hypoechoic nodules on thyroid ultrasonography in a prepubertal child | |
| • Psammomatous melanotic schwannoma[a] | |
| • Blue nevus, epithelioid blue nevus (multiple)[a] | |
| • Breast ductal adenoma (multiple)[a] | |
| • Osteochondromyxoma | |
| Supplemental criteria: | 1. Affected first-degree relative |
| | 2. Inactivating mutation of the *PRKAR1A* gene |

*CNC* Carney complex, *PPNAD* primary pigmented nodular adrenocortical disease, *GH* growth hormone, *LCCSCT* large-cell calcifying Sertoli cell tumour [a] Histological confirmation is needed

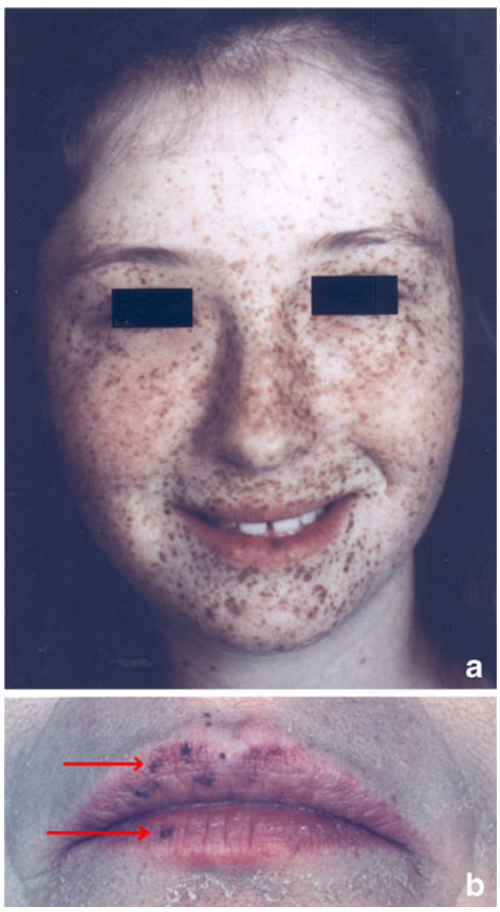


**Fig. 1** **a** Cutaneous and mucocutaneous pigmentation of a 9-year-old girl with CNC. Multiple non-elevated brown-black spots on the face, the vermilion borders of lips, and the upper eyelid are noticed. **b** Characteristic pigmentation (*red arrows*) of the vermilion borders of lips in a patient with CNC

*Pathological features*

Histologically, epithelioid blue nevi are characterised by short fascicles, small nests and single, round or spindle-shaped melanocytes with dendritic, pigmented, elongation processes in the upper dermis. Mitotic activity is rare.

Skin myxomas

*Clinical features*

Skin myxomas are a major component of CNC, present in 33 % of the patients and occur on the eye lid (the most common site), the external ear canal, the nipple and the oropharynx (Fig. 3a) [5]. Their appearance varies from small (3 mm in diameter), opalescent or dark pink sessile

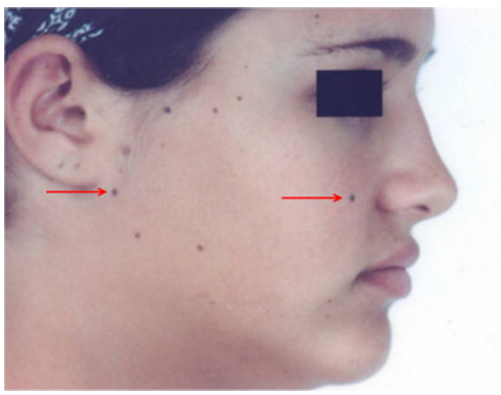

**Fig. 2** Multiple, non-elevated lesions (*red arrows*), consistent with epithelioid blue-nevi, are depicted on the face of a patient with CNC. They are blue to black in colour and bigger in size than spotty skin pigmentation

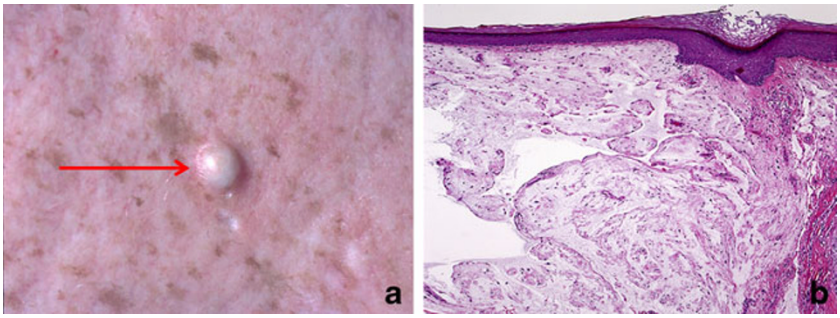


**Fig. 3** **a** Skin myxoma (*red arrow*) of a patient with CNC. The lesion is small and opalescent. **b** A subcutaneous myxoma (5× magnification, H&E stain). There is a somewhat circumscribed, non-encapsulated nodule in the dermis, composed of bland stellate and short spindle-shaped cells in a myxoid (mucinous) stroma with prominent small blood vessels. The overlying epidermis show attenuated rete ridges and slight compact hyperkeratosis

papules, to large (up to 5 cm) pedinculated lesions with a finger-like appearance.

*Pathological features*

Skin myxomas consist of basophilic ground substance (myxoid stroma) with few macrophages or bland spindle cells, forming poorly or well-lobulated dermal masses with widely spaced capillaries (Fig. 3b).

## Heart lesions

Heart myxomas

*Clinical features*

Among CNC patients, heart myxomas occur at any age (median age at detection, 20 years), although at a younger age when compared with sporadic cardiac myxomas. They may be multicentric and can be found in all cardiac chambers [5, 19]. The presenting signs and symptoms derive from cardiac or embolic events, such as embolic strokes. Heart myxomas and emboli deriving from them are the main cause of morbidity and mortality of CNC patients. Frequently, CNC patients with heart myxomas have two or more operations for recurrent tumours [19, 20].

*Pathological features*

Heart myxomas usually have a papillary or smooth surface, with a narrow or wide pedicle and gelatinous or haemorrhagic appearance (Fig. 4). The entire tumour is covered by endothelium and is composed of a rich mucoid matrix ("myxoma" cells, frequently multinuclei, arranged in nests or in columns), along with mesenchymal, mastoid and inflammatory cells.

*Radiological features*

Heart myxomas range from a few millimetres to 8 cm in diameter and can be partially calcified. On sonography, heart myxomas present as isoechoic (compared with the heart wall) masses inside the cardiac chambers (Fig. 5a). On T2-weighted magnetic resonance imaging (MRI) studies, myxomas appear as hyperintense lesions compared with the myocardium (Fig. 5b).

## Endocrine lesions

Pituitary gland: growth hormone (GH)-secreting and prolactin (PRL)-secreting adenomas

The incidence of GH-producing pituitary tumours and clinical acromegaly has been estimated at less than 15 % in patients with CNC [10, 21]. However, abnormal response of GH to oral glucose tolerance test and "paradoxical" response to stimuli, such as thyrotropin-releasing hormone (TRH), without a detectable tumour in MRI studies, may be present in up to 80 % of the patients [22]. Acromegaly, when present, is generally characterised by a slow, progressive clinical course.

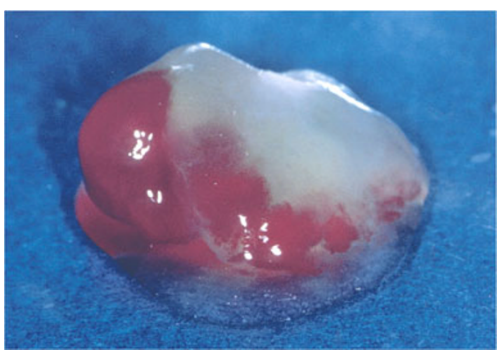

**Fig. 4** Heart myxoma of a patient with CNC. The tumour has a smooth gelatinous surface with haemorrhagic appearance

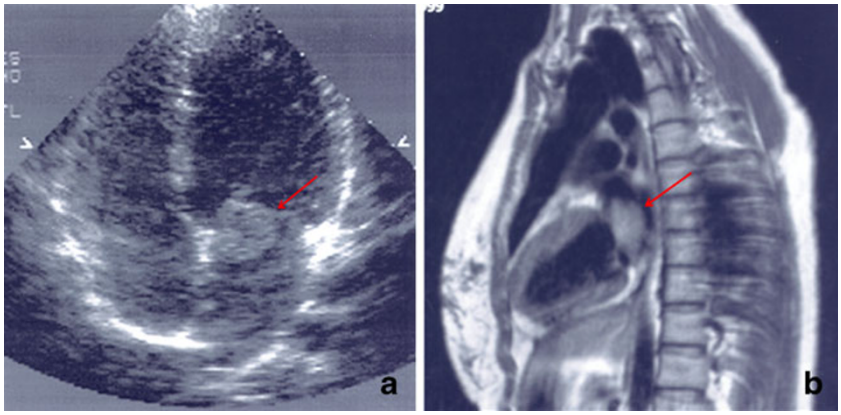


**Fig. 5** **a** Echocardiogram of the same patient, which shows an echogenic hyperechoic tumour within the left atrium (*red arrow*). **b** Sagittal view of a T2-weighted MR image, which shows a hyperintense tumour (*red arrow*) located within the left atrium corresponding to the heart myxoma

Patients presenting with acromegaly as the primary manifestation of the CNC usually have pituitary macroadenomas (tumour size bigger than 10 mm).

*Pathological features*

The histology reports from CNC patients operated on for pituitary tumours suggest that the pituitary adenomas are usually surrounded by a hyperplastic transition zone and multiple tumours are concurrently present. This finding, along with data from genetic studies of the adenomas, supports the concept that each adenoma stems from clonic undifferentiation of hyperplastic pituitary cells [21]. The adenomas usually stain positive for GH and PRL, and occasionally for α-subunit, β-TSH and β-LH [21].

*Radiological features*

In a study where patients were followed-up prospectively, increased levels of GH and PRL were usually found before the radiological detection of the tumour [21]. In the majority of these cases, the tumours were microadenomas (greatest diameter less than 1 cm) and the radiological assessment of the pituitary gland was negative [21, 23, 24].

Thyroid gland: adenomas, carcinomas

*Clinical features*

In the biggest published series to date with sonographic evaluation of patients with the complex, ultrasonography revealed some thyroid pathology in almost 60 % of all patients, and 67 % among children and adolescents [25]. This comes in contrast with the detection rate of unsuspected nodules in the general population which varies from 17 to 19 % in men, 20–44 % in women and up to 1.8 % in children [26–28]. Hence, CNC patients, despite the sonographic findings, usually remain clinically and biochemically euthyroid (levels of T4, Free T4, T3, and TSH remain within normal limits) [25].

*Pathological features*

The thyroid gland abnormalities in patients with CNC, display a broad spectrum of presentations, including follicular hyperplasia and/or cystic changes, and rarely progress to carcinomas [5, 10, 25, 29]. On biopsy, the most common finding is benign follicular adenomas. Thyroid carcinoma is unusual among CNC patients, but when present, it is of follicular or papillary type (Fig. 6) [25]. On the contrary, thyroid cancer associated with MEN syndromes is medullary carcinoma.

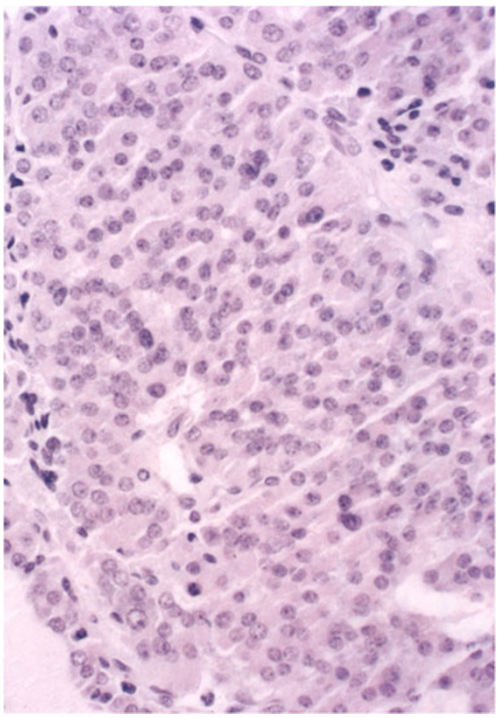

**Fig. 6** Histological picture of thyroid lesion of a patient with CNC. The tumour is composed of solid sheets of cells with rounded nuclei, inconspicuous nucleoli, and moderate to abundant eosinophilic cytoplasm

*Radiological features*

On sonography, the thyroid gland size is usually within normal limits. Pathological findings consist of small, hypoechoic, solid, cystic or mixed, lesions (nodules) surrounded by thyroid tissue of normal texture (Fig. 7a). Lesions are usually multiple and bilateral. Malignant nodules are usually bigger than 10 mm, hypoechoic and demonstrate accelerated growth between sequential evaluations (Fig. 7b) [25]. Lymphadenopathy in cases of carcinomas is rare. Sonographic evaluation is recommended to be included in the screening protocols of CNC patients, and any growing nodule, especially in patients with multifocal and bilateral disease, should be biopsied, even when they present with benign sonographic characteristics [3, 25].

Adrenal glands: primary pigmented nodular adrenocortical disease (PPNAD)

*Clinical features*

PPNAD is a generally rare cause of adrenocorticotropin hormone (ACTH)-independent Cushing's syndrome, but it is observed in almost 25–30 % of CNC patients. However, histological evidence of PPNAD has been reported in almost every patient with CNC who underwent an autopsy [5]. PPNAD usually presents in the 2nd or 3rd decade of life, without demonstrating the strong female predilection seen in adult patients with Cushing's syndrome [30]. The disease is named after the small, cortisol producing, pigmented micronodules seen in the adrenal cortex [31]. The hypercortisolism may manifest as the classic constellation of Cushing's characteristics or with isolated features, like mild growth retardation (short stature), severe precocious osteoporosis and severe muscle and skin wasting [30]. Cyclical or atypical Cushing's syndrome is also common among patients with CNC [30]. Biochemically, the blood and urinary cortisol levels are elevated, while ACTH levels are low if not undetectable. In Liddle's test (using low and high doses of dexamethasone), these patients usually present with a paradoxical increase of urinary free cortisol and 17-hydroxycorticosteroid levels on the 2nd day of administration of high doses of dexamethasone [32]. The recommended treatment for patients with PPNAD is bilateral adrenalectomy [33, 34].

*Pathological features*

Macroscopically, adrenals, are usually small or slightly enlarged in size, with multiple dark brown or black nodules from 0.5 to 5 mm which correspond to the "nodular pigmentation" (Fig. 8). Microscopically, adrenals have: (1) numerous non-encapsulated cortical nodules containing large amount of lipofuscin, responsible for their black appearance and (2) a pathognomonic atrophy of the remaining cortex, as opposed to the hyperplastic cortex usually observed between adenomas in patients with pituitary-dependent Cushing's disease (Fig. 9).

*Radiological features*

PPNAD remains a diagnostic challenge for the radiologist due to: (1) the small overall size, if not atrophy, of the affected adrenals and (2) the small size of the pigmented nodules (0.5–3 mm, in patients less than 10 years old) [1, 33]. Usually, CT images obtained with slice thickness of 5 or 10 mm in patients with PPNAD are reviewed as normal. If CT examinations are obtained with slice thickness of 3 mm or less, before and after IV injection of contrast material, numerous lesions (pigmented nodules) appear. The pigmented nodules are small (<3 mm), round, well delineated and always hypodense (in the pre- and post-contrast studies) compared with the rest of the adrenal parenchyma. Macronodular hyperplasia (nodules bigger than 10 mm) is rare among patients with the complex. Indicative imaging signs of PPNAD are: (1) any subtle

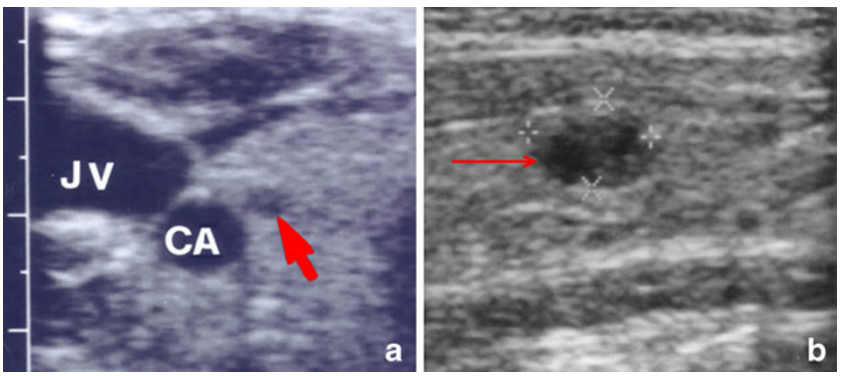


**Fig. 7** **a** Sonography image demonstrating a small round hypoechoic nodule at the right lobe of the thyroid gland of a patient with CNC (*red arrow*). The lesion corresponds to an adenomatous nodule (*CA* carotid artery, *JV* jugular vein). **b** Sonography image demonstrating an ovoid hypoechoic nodule (*red arrow*) of the thyroid gland in a patient with CNC. Fine-needle aspiration (FNA) was consistent with thyroid carcinoma, follicular type

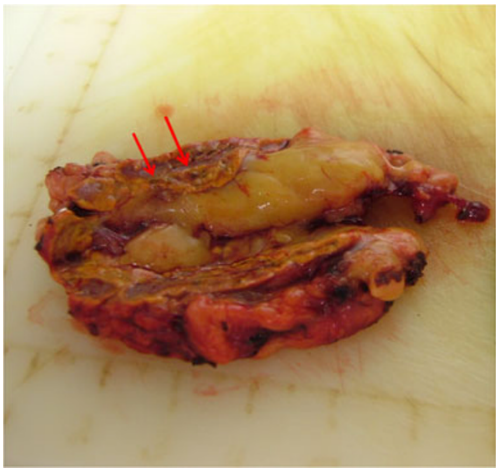

**Fig. 8** Gross specimen of left adrenal in a patient with CNC and PPNAD. The adrenal is of normal size. Multiple small black nodules are seen (*red arrows*)

contour abnormality and (2) the presence of one or more hypodense spots (in pre- and post-contrast studies) within the gland. Doppman et al. [35] reported that: "…adrenal glands of normal dimensions but with a knobbly or irregular contour in a young patient who initially has Cushing's syndrome or severe osteoporosis should suggest the diagnosis of PPNAD". Thus, high-resolution pre- and post-contrast CT studies, obtained with slice thickness of 3 mm or less, are required for the evaluation of patients clinically suspicious for PPNAD (Fig. 10).

## Breast lesions

Two different breast tumours, which can coexist, have been reported in CNC patients: (1) myxoid fibroadenomas ("breast myxomatosis"), which are abnormalities of the mesenchyma, and (2) ductal adenomas (DAs), which are abnormalities of the epithelium [36, 37]. Myxoid fibroadenomas and DAs are benign and no malignant transformation has been reported among CNC patients [36, 38]. However, the possibility that the benign hyperplastic lesions progress to malignant ones cannot be excluded. Additionally, the presence of these lesions usually complicates the mammographic screening of patients with CNC for breast cancer, because of their multiplicity and the similar imaging characteristics.

### Myxoid fibroadenomas or "breast myxomatosis"

#### *Clinical features*

The physical examination of the breast with myxoid fibroadenomas is significant for diffuse nodularity without dominant masses, probably due to the young age of the examined patients (3rd or 4th decade of life). None of the known patients with isolated myxoid fibroadenomas has been reported to have blood nipple discharge, breast skin abnormalities or sentinel lymphadenopathy [38]. The lesions present bilaterally and multifocally in almost 40 % of the patients [36].

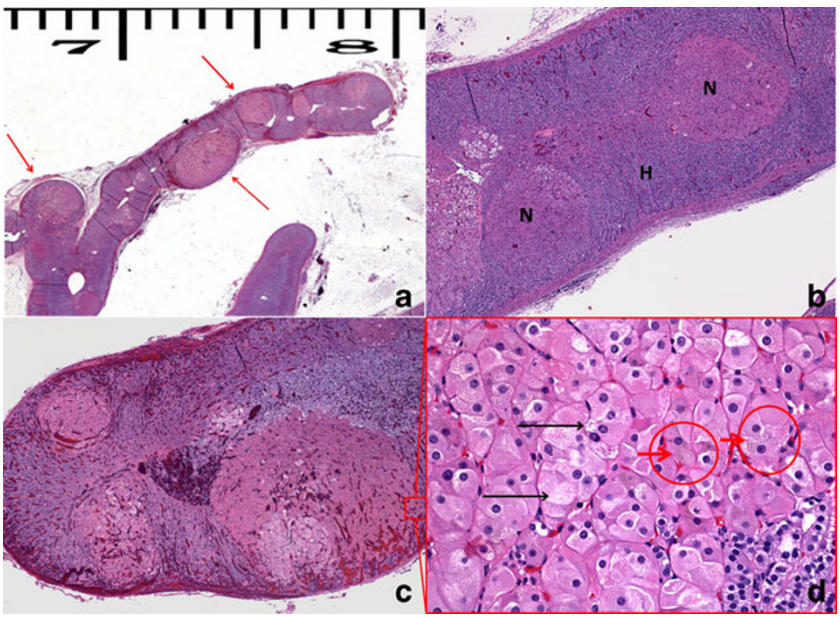


**Fig. 9** **a** Picture from the adrenal gland from a patient with PPNAD with characteristic preservation of the normal gland shape. Multiple nodules (*red arrows*) throughout the cortex, that barely distort the outline of the gland, give it the characteristic picture of "beads on a string". **b** Another magnification (2.5×) of the same adrenal gland showing multiple nodules and diffuse hyperplasia (*N* nodule, *H* hyperplasia). **c** Another view (2.5× magnification) of the adrenal gland showing how nodules can coalesce in this view there is little hyperplastic cortex and even atrophy. The preservation of the medulla is also shown. **d** One of the nodules at 20× magnification (*red box* from picture **c**) showing cells filled with lipids (*black arrows*), characteristic of the steroidogenesis, and lipofuscin (*red arrows*)

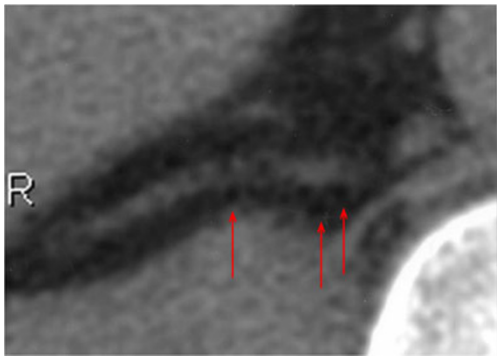


**Fig. 10** Patient with CNC and PPNAD. Unenhanced CT image (slice thickness of 3 mm) of the right adrenal shows multiple, small, round hypodense areas (*red arrows*) corresponding to pigmented nodules

*Pathological features*

In myxoid fibroadenomas, myxoid material is accumulated in the stroma of single or small groups of nodules. Large aggregates of these lesions form the myxoid fibroadenomas (Fig. 11) [36].

*Radiological features*

The number of myxoid lesions depicted with MR mammography is significantly superior to the lesions depicted with sonography or conventional mammography in CNC patients. The masses that are detected with mammogram are well defined, non-calcified, isodense or hypodense compared with the breast parenchyma. Even though it is well known that fibroadenomas can produce "coarse" calcifications, this is not described in the biggest reported series with CNC cases [38]. The sonographic demonstration of myxoid fibroadenomas varies from solid, well-circumscribed, ovoid in shape, hypoechoic masses to complex cystic lesions (Fig. 12). Small (less than 6 mm) myxoid fibroadenomas may have an irregular contour, which is not consistent with benign lesions [38]. In such cases, fine-needle aspiration (FNA) is strongly recommended, even in a proven CNC patient. It is reported that fat-suppressed, fast spin-echo, T2 sequence demonstrates most of the breast myxoid fibroadenomas as high-signal intensity masses [38]. Myxoid fibroadenomas revealed with this method are usually numerous (more than 58 per breast in a case). This situation is referred to as "breast myxomatosis" and is characteristic for the CNC (Fig. 13). Even though, the MRI appearance of myxoid lesions is not characteristic, their multiplicity, their shape similarity and the homogeneous increase of the signal intensity are consistent with a benign pathological entity [38]. Also, routine chest MRI examination, using inversion recovery sequence, can reveal numerous hyperintense breast lesions corresponding to myxoid fibroadenomas [38].

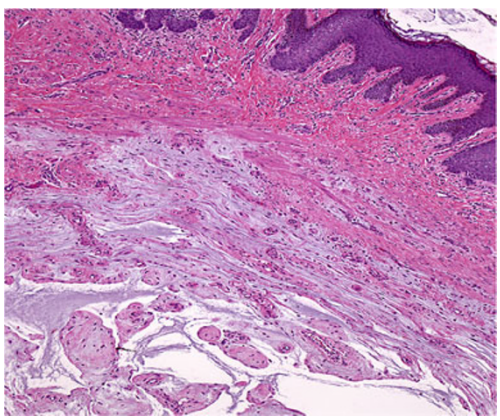

**Fig. 11** A breast myxoma at 5× magnification. There is a non-encapsulated lesion in the reticular dermis, composed of bland stellate and short spindle-shaped cells in a myxoid (mucinous) stroma with prominent small blood vessels. The overlying epidermis show slight mild acanthosis. There is no significant involvement of the papillary dermis

Ductal adenomas (DAs)

The ductal adenomas of the breast were first reported by Azzopardi and Salm in 1984 [39]. It should be noticed that in that series, due to clinical (presentation in older patients), imaging (presence of suspicious microcalcifications), and pathological findings (cellularity and complexity pattern with invasion of the tumour capsule), these tumours were misinterpreted as breast carcinomas and two of those patients underwent radical mastectomy [39]. Therefore, it is important to recognise DAs for two reasons. First, to avoid their misinterpretation as breast carcinoma and second, because they are a characteristic pathological entity for CNC as described by Carney and Toorkey [37]. The presentation of DA could be even the primary manifestation of the complex.

*Clinical features*

Usually, DAs are palpable, painless masses near the areola, which can be asymptomatic or manifest as blood nipple discharge.

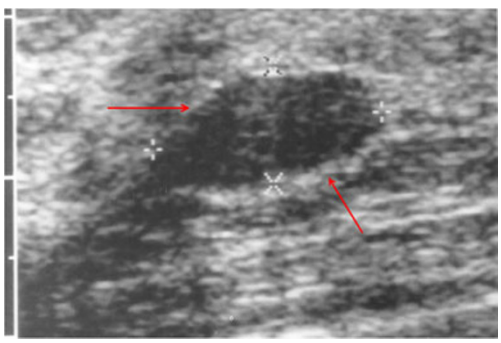

**Fig. 12** Female patient with CNC. Sonography of the right breast demonstrates a solid, ovoid in shape, well circumscribed, hypoechoic lesion (*red arrow*). FNA was consistent with myxoid fibroadenoma

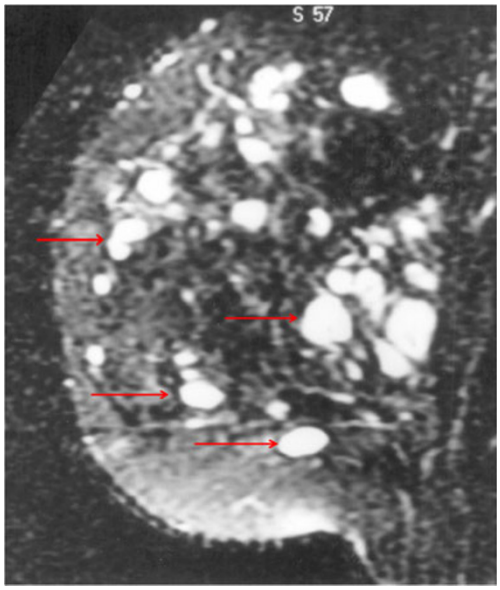


**Fig. 13** Female patient with CNC and breast myxomatosis. MR image: sagittal, fat suppressed fast spin echo T2-weighted image demonstrates numerous hyperintense nodules corresponding to myxoid fibroadenomas (*red arrows*)

*Pathological features*

DAs involve ducts and are covered by a thick capsule of hyalinised fibrous tissue, which sometimes contains dystrophic calcifications. The shape of the tumour can be well delineated and spherical or completely irregular, with a diameter ranging from 10 to 40 mm. Their essential cellular components are (1) non-branching tubules of different size lined by epithelial and myoepithelial cells and (2) connective tissue (Fig. 14).

*Radiological features*

DAs present as soft tissue tumours with well-defined or unclear margins, and they always contain calcifications [38]. Calcifications seen in DA do not have a uniform appearance. Coarse calcifications (typically benign) or microcalcifications simulating adenocarcinoma have been described (Fig. 15) [38]. The differential diagnosis is difficult, and the presence of other CNC components or the coexistence of myxoid fibroadenomas in the same or the opposite breast can be helpful. FNA is always required.

## Male genitalia lesions

Primarily large-cell calcifying sertoli cell tumour (LCCSCT)

The most frequent testicular manifestation in the CNC is the LCCSCT, although Leydig cell tumours and nodular

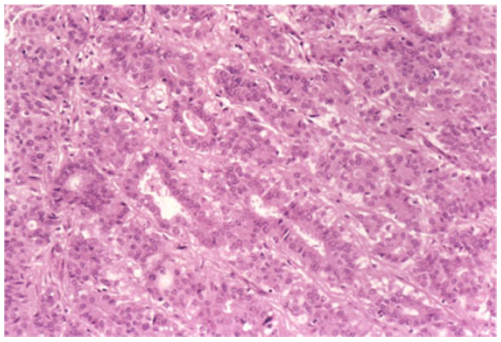

**Fig. 14** Photomicrograph (original magnification, 200×; H&E stain) of a ductal adenoma specimen shows roughly parallel longitudinally and transversely sectioned tubules in fibrous stroma. The tubules are lined by a single row of uniform epithelial cells with vesicular nuclei and eosinophilic cytoplasm. There is secretion in a number of the tubular lumens

adrenocortical rest tissue have also been reported [5]. LCCSCTs are almost always found by ultrasonography in post-pubertal male patients with CNC, although the age at diagnosis ranges from 2 to 51 years old [10, 40]. LCCSCTs have also been reported in patients with Peutz-Jeghers syndrome, underlining furthermore the similarity of these two syndromes [17]. The

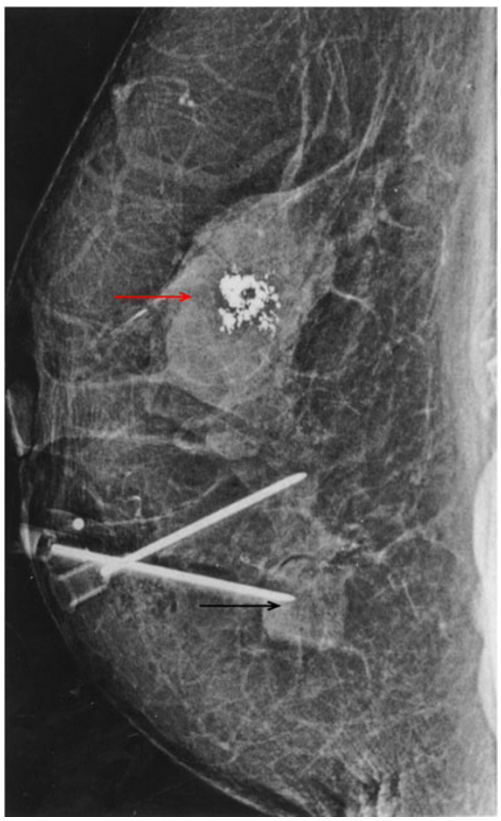

**Fig. 15** Female patient with CNC. Mammography demonstrates two low density masses. The larger mass (*red arrow*) with clusters of punctuate calcifications is a histopathologically proven ductal adenoma. The other mass is a fibroadenoma (*black arrow*) (reproduced with permission from reference [37])

initial treatment applied to these patients was tumour enucleation or partial orchiectomy [40]. However, the current recommendations suggest annual sonographic follow-up and measurement of testicular tumour markers for patients with CNC and LCCSCT, because of the potential risk for malignant transformation [5, 10].

Clinical features

LCCSCTs, often bilateral and multicentric, are usually asymptomatic, but can rarely present with precocious puberty or gynaecomastia. Men with CNC are also at increased risk for infertility [40, 41]. In clinical examination, tumours, when palpable, are often felt as hard non-tender masses.

Pathological features

LCCSCT is a stromal tumour composed of large Sertoli cells of different morphology (cuboidal, columnar, or round) arranged in groups. Multiple foci of calcifications are the prominent and characteristic finding of the tumour (Fig. 16).

Radiological features

In the sonographic evaluation of the testis, LCCSCTs have some pathognomonic features: (1) they are almost always bilateral, (2) they contain multiple "coarse" calcifications with smooth contour and broad acoustic shadowing and (3) there is no soft tissue component (Fig. 17) [40].

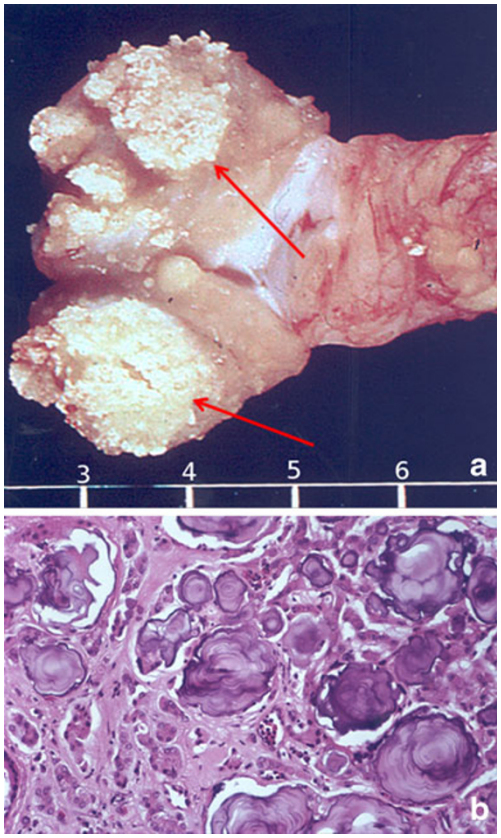


**Fig. 16** **a** A 6-year-old patient with CNC and LCCSCT. Gross pathology demonstrates characteristic multiple foci of coarse calcifications in the testis (*red arrows*). **b** The tumour is composed of sheets, cords, and solid tubules of cells with abundant fibrous tissue that contains large areas of calcification

## Female genitalia lesions

Myxomas, ovarian cysts, ovarian carcinomas

*Clinical features*

Carcinomas of the ovarian surface epithelium have been identified in 1.12 % of female patients with CNC, whereas the reported incidence of ovarian cancer among American women is 0.015 % [42, 43]. In an autopsy series of 12 female patients affected by the complex, 58 % were found to have an ovarian lesion, while 67 % of women with CNC participating in a prospective sonographic study had at least 1 ultrasound study positive for ovarian cysts [42]. Non-stromal tumours (like in Peutz-Jeghers syndrome) have also been reported among patients with the complex [44].

*Radiological features*

The sonographic findings have no characteristic feature and are similar to the non-specific multilocular ovarian lesions usually seen in the general population. Ultrasound of the ovaries may be part of the initial evaluation in female patients with CNC; follow-up of any identified lesion is recommended, because of the possible risk for malignancy [5].

## Peripheral nerve tumours

Psammomatous melanotic schwannoma (PMS)

*Clinical features*

PMSs have no characteristic clinical sign, symptom, or imaging finding. They occur commonly in the gastrointestinal tract (favouring the stomach), in the spinal nerve roots and can rarely involve the trigeminal nerve, also eroding the bones [45]. Another not uncommon site is the chest wall with involvement of adjacent ribs. PMSs, as classic schwannomas, can also involve the spinal nerves, when they are located in their posterior root [46]. PMSs are potentially malignant and cases of patients dying from metastasis have been described [4].

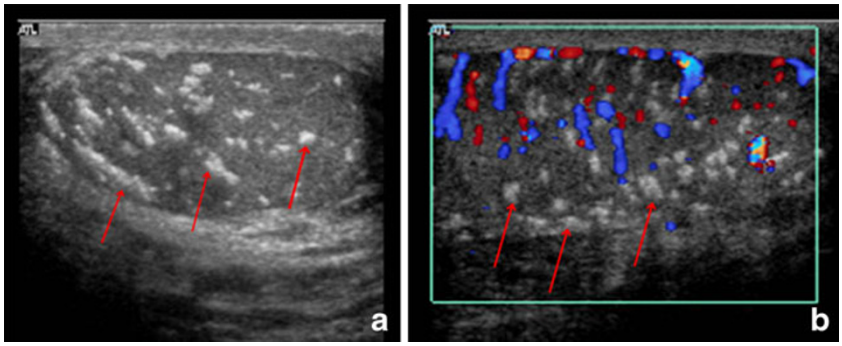


**Fig. 17** Sonographic image of the testis demonstrates the characteristic coarse multiple calcifications (*red arrows*) in the parenchyma in a young patient with CNC and LCCSCT

*Pathological features*

Schwannoma is a benign encapsulated tumour of peripheral nerve sheath which consists of Schwann cells, but rarely contains melanin or psammoma bodies (Fig. 18a). Pathognomonically, PMS of CNC patients contains melanin and psammoma bodies (Fig. 18b) [45, 46].

*Radiological features*

PMSs have different roentgenographical patterns, depending on their size and location. When they are close to the long bones, they cause significant cortical erosion. PMS of the nerves of the chest wall can involve the adjacent ribs and present as calcified soft tissue mass with osteolytic and osteosclerotic areas. PMSs can also cause severe destruction of the body of a vertebra mimicking metastatic lesion of unknown primary site. On CT and MR images, PMSs of the spine are demonstrated as soft-tissue tumours with "dumbbell" morphology, with bone erosion and reactive osteosclerosis. An enlargement of the intravertebral foramina is not uncommon. Mass effects, like stenosis of the spinal canal or displacement of the spinal cord, depend on tumour size and anatomic location (Fig. 19).

**Bone lesions**

Osteochondromyxoma or "Carney bone tumour"

Although congenital bone tumours are very rare, an unusual type, osteochondromyxomas, may present within the context of CNC [47, 48]. Only a few cases have been described until now and none of them has metastasised, even though some cases presented with osteolytic appearance [48].

Clinical features

In all reported patients, osteochondromyxomas were painless. Tumours were detected during the imaging evaluation of mass side effects, like proptosis, nasal obstruction, or painless swelling [48].

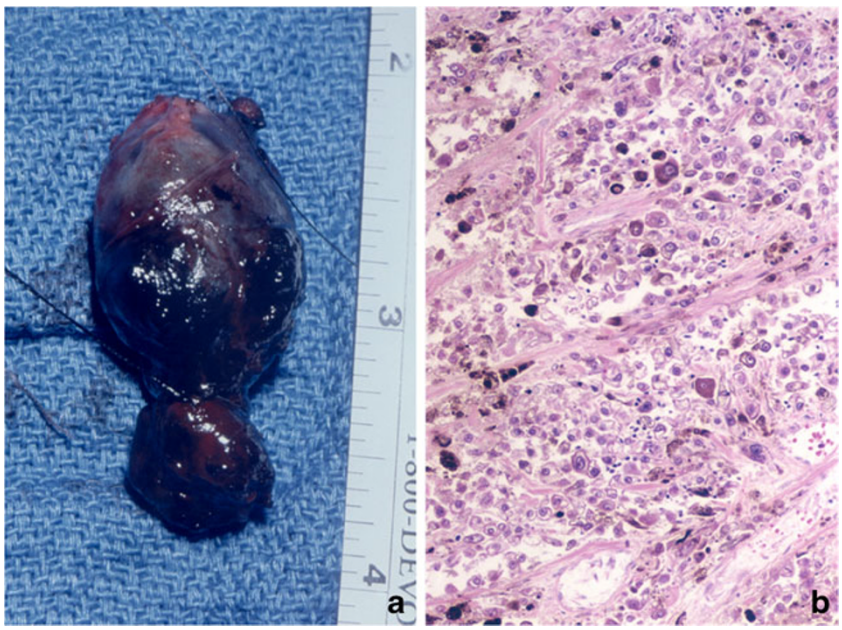


**Fig. 18** **a** Gross specimen of an encapsulated psammomatic melanotic schwannoma. **b** The tumour is composed of plump spindle to epithelioid cells arranged in sheets, lobules and interlacing fascicles. Lesional cells contain rounded to ovoid nuclei, small nucleoli and variable cytoplasmic pigmentation. Scattered pigmented melanophages are present throughout the tumour

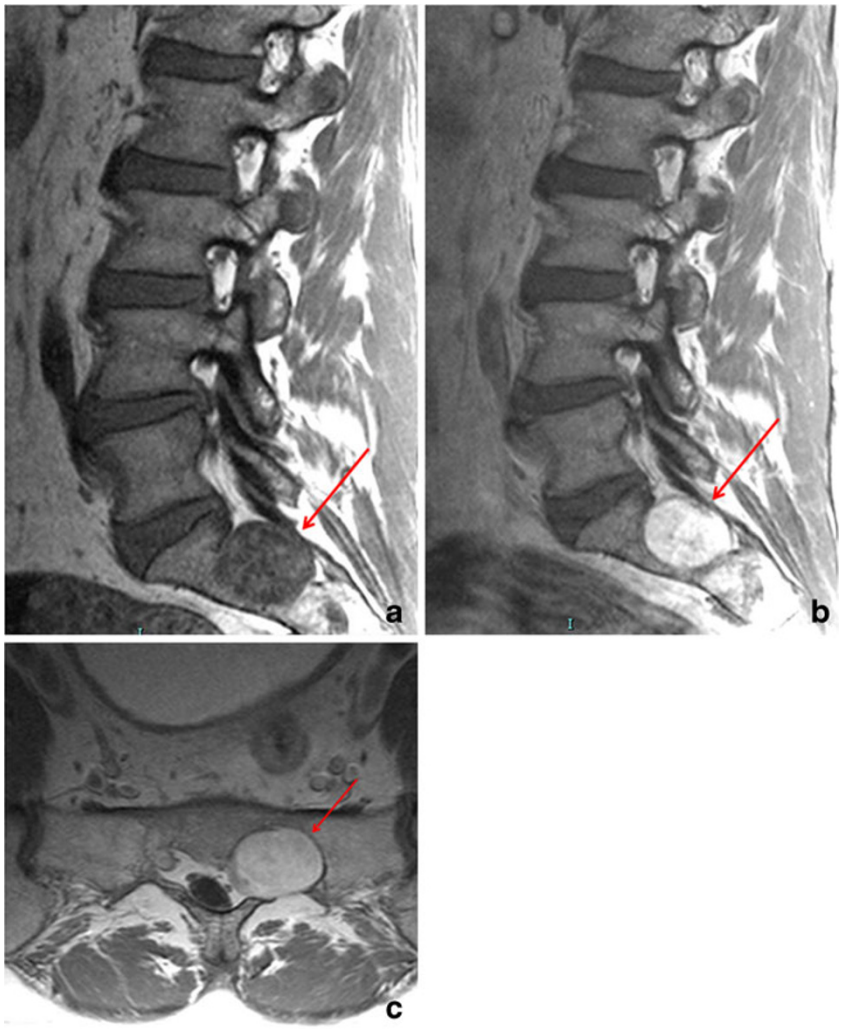


**Fig. 19** **a**, **b** MR images of a psammomatic melanotic schwannoma of the spine in a patient with CNC (*red arrows*). **c** Axial T2-weighted image of the spine shows a mass lesion with intermediate signal intensity and "dumbbell" morphology causing enlargement of the intravertebral foramina (*red arrow*)

## Pathological features

Osteochondromyxomas have been described as circumscribed, unencapsulated, osteolytic lesions involving the adjacent soft tissues and composed of "myxoid" matrix, hyaline fibrous tissue, and cartilage and bone elements (Fig. 20). The proportions of the multiple cell types and amounts of the different tissue matrices vary significantly from region to region within the same tumour [48].

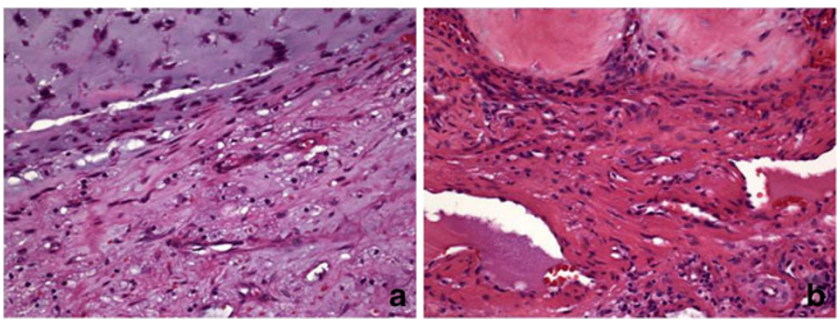


**Fig. 20** H&E stain of bone lesions that were excised from two patients with CNC. **a** Zone of moderately cellular hyaline cartilage in a background of hypocellular vascularised myxoid tissue, characteristic of an osteochondromyxoma. **b** Two islands of hypocellular hyaline cartilage in a moderately cellular spindle cell stroma containing a few dilated blood vessels, characteristic of the cartilage component of the bone lesions seen in the context of CNC

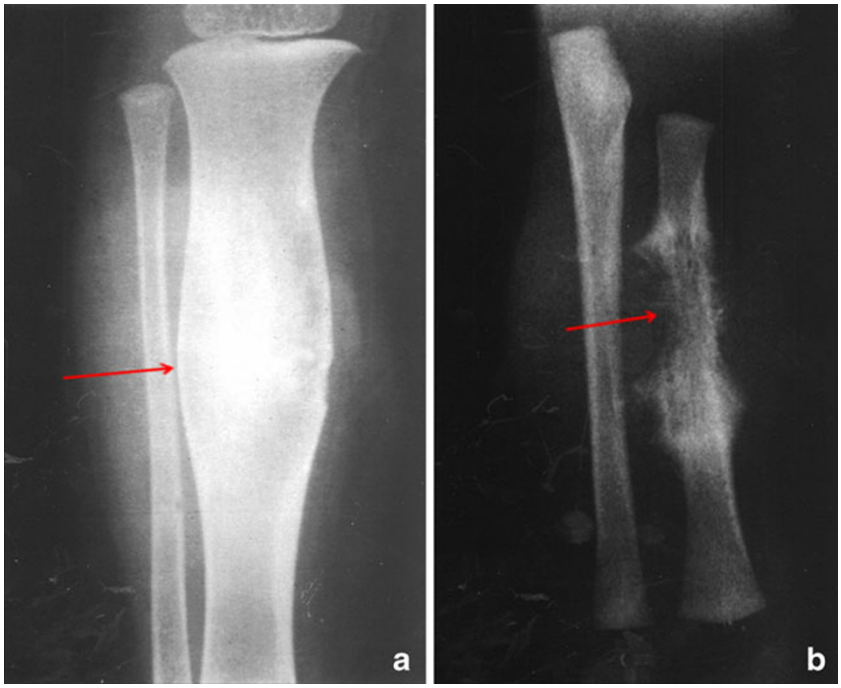


**Fig. 21** **a** Expansile, mixed lucent and sclerotic lesion of the tibial diaphysis (*red arrow*). A defect in the medial cortex is consistent with a biopsy site. There is abnormal tubulation of the tibia and fibula. (reproduced from [48] with permission). **b** Permeative, lytic diaphyseal lesion (*red arrow*) of the radius with aggressive periosteal new bone formation and associated soft tissue mass

## Radiological features

Osteochondromyxomas do not have a uniform radiographical appearance [48]. When they are located in the long bones, they can present as a permeative lytic periosteal lesion with aggressive new bone formation, or as an expansile bone area with sclerotic and lucent regions (Fig. 21). Radiographical differential diagnosis from other bone tumours should include

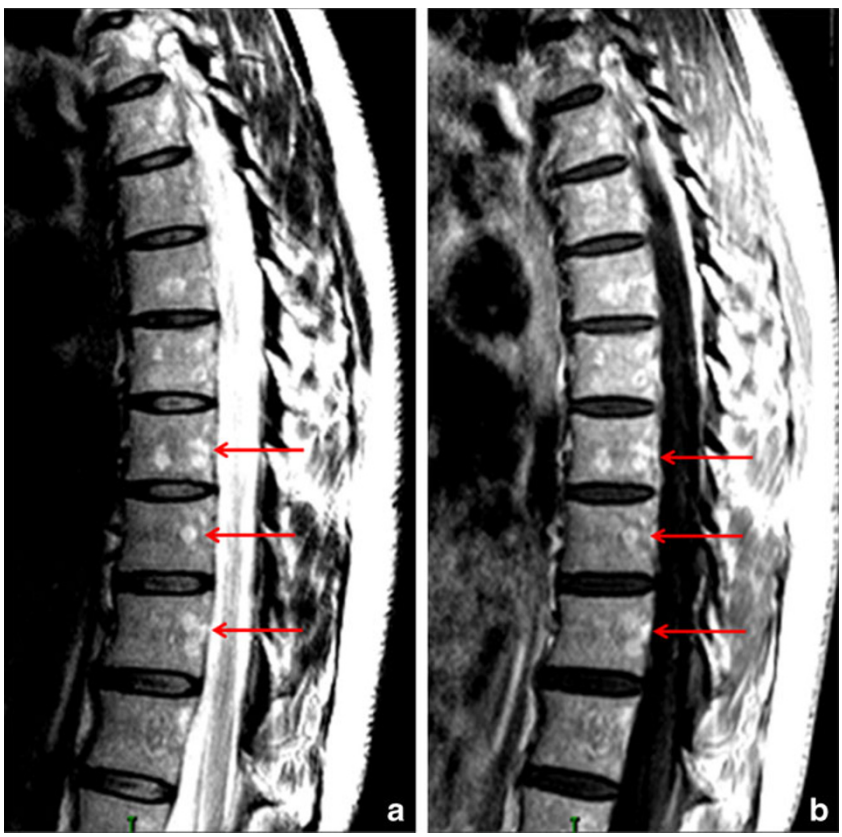


**Fig. 22** MRI scans of osteochondromyxoma. Sagittal T2-weighted (**a**) and post-contrast (**b**) image of osteochondromyxomas in a female patient with CNC. On T2-weighted scan (**a**), there are abnormal focal areas with slightly increased signal (*red arrows*), and on the post-contrast scan (**b**) they demonstrated mild enhancement (*red arrows*). The imaging findings are consistent with a fibro-osteotic nature, differentiating them from other common lesions of the spine (i.e. haemangiomas, schwannomas)

chondromyxoid fibroma, mesenchymal hamartoma (mesenchymoma), myxoma, chondrosarcoma with myxoid change and fibrocartilaginous mesenchymoma. On MRI, osteochondromyxomas of the spine appear as areas with slightly increased signal on T2-weighted images, showing slight enhancement on post-contrast studies (Fig. 22).

## Conclusion

The CNC may present with symptoms from a variety of different tissues and can mimic isolated diseases or other syndromes. The recognition of the strong association of certain manifestations with the complex and the specific constellation of symptoms that these patients experience is important for establishing the appropriate diagnosis and treatment.



## References

1. Carney JA (1985) The complex of myxomas, spotty skin pigmentation and endocrine overactivity. Medicine 64(4):270–283
2. OMIM (12/10/2010) MIM number: #160980. Johns Hopkins University, Baltimore, MD. World Wide Web URL: http://omimorg/
3. Rothenbuhler A, Stratakis CA (2010) Clinical and molecular genetics of Carney complex. Best Pract Res Clin Endocrinol Metab 24(3):389–399
4. Bertherat J, Horvath A, Groussin L, Grabar S, Boikos S, Cazabat L, Libe R, Rene-Corail F, Stergiopoulos S, Bourdeau I, Bei T, Clauser E, Calender A, Kirschner LS, Bertagna X, Carney JA, Stratakis CA (2009) Mutations in regulatory subunit type 1A of cyclic adenosine 5′-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. J Clin Endocrinol Metab 94(6):2085–2091
5. Stratakis CA, Kirschner LS, Carney JA (2001) Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab 86(9):4041–4046
6. Casey M, Mah C, Merliss AD, Kirschner LS, Taymans SE, Denio AE, Korf B, Irvine AD, Hughes A, Carney JA, Stratakis CA, Basson CT (1998) Identification of a novel genetic locus for familial cardiac myxomas and Carney complex. Circulation 98 (23):2560–2566
7. Stratakis CA, Carney JA, Lin JP, Papanicolaou DA, Karl M, Kastner DL, Pras E, Chrousos GP (1996) Carney complex, a familial multiple neoplasia and lentiginosis syndrome. Analysis of 11 kindreds and linkage to the short arm of chromosome 2. J Clin Invest 97(3):699–705
8. Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA (2000) Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. Nat Genet 26(1):89–92
9. Bossis I, Stratakis CA (2004) Minireview: PRKAR1A: normal and abnormal functions. Endocrinology 145(12):5452–5458
10. Boikos SA, Stratakis CA (2007) Carney complex: the first 20 years. Curr Opin Oncol 19(1):24–29
11. Boikos SA, Stratakis CA (2006) Carney complex: pathology and molecular genetics. Neuroendocrinology 83(3–4):189–199
12. Horvath A, Bertherat J, Groussin L, Guillaud-Bataille M, Tsang K, Cazabat L, Libe R, Remmers E, Rene-Corail F, Faucz FR, Clauser E, Calender A, Bertagna X, Carney JA, Stratakis CA (2010) Mutations and polymorphisms in the gene encoding regulatory subunit type 1-alpha of protein kinase A (PRKAR1A): an update. Hum Mutat 31(4):369–379
13. Chrousos GP, Stratakis CA (1998) Carney complex and the familial lentiginosis syndromes: link to inherited neoplasias and developmental disorders, and genetic loci. J Intern Med 243(6):573–579
14. Stratakis CA (2000) Genetics of Carney complex and related familial lentiginoses, and other multiple tumor syndromes. Front Biosci 5:D353–D366
15. Stratakis CA, Kirschner LS, Taymans SE, Tomlinson IP, Marsh DJ, Torpy DJ, Giatzakis C, Eccles DM, Theaker J, Houlston RS, Blouin JL, Antonarakis SE, Basson CT, Eng C, Carney JA (1998) Carney complex, Peutz-Jeghers syndrome, Cowden disease, and Bannayan-Zonana syndrome share cutaneous and endocrine manifestations, but not genetic loci. J Clin Endocrinol Metab 83 (8):2972–2976
16. Stratakis CA (2001) Clinical genetics of multiple endocrine neoplasias, Carney complex and related syndromes. J Endocrinol Investig 24(5):370–383
17. Stratakis CA (2000) Genetics of Peutz-Jeghers syndrome, Carney complex and other familial lentiginoses. Horm Res 54(5–6):334–343
18. Stratakis C (1999) Carney complex and related syndromes and their genetic loci—author's response. J Clin Endocrinol Metab 84 (4):1491–1492
19. McCarthy PM, Piehler JM, Schaff HV, Pluth JR, Orszulak TA, Vidaillet HJ Jr, Carney JA (1986) The significance of multiple, recurrent, and "complex" cardiac myxomas. J Thorac Cardiovasc Surg 91(3):389–396
20. Carney JA (1995) Carney complex: the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas. Semin Dermatol 14(2):90–98
21. Pack SD, Kirschner LS, Pak E, Zhuang Z, Carney JA, Stratakis CA (2000) Genetic and histologic studies of somatomammotropic pituitary tumors in patients with the "complex of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas" (Carney complex). J Clin Endocrinol Metab 85(10):3860–3865
22. Boikos SA, Stratakis CA (2006) Pituitary pathology in patients with Carney Complex: growth-hormone producing hyperplasia or tumors and their association with other abnormalities. Pituitary 9 (3):203–209
23. Watson JC, Stratakis CA, Bryant-Greenwood PK, Koch CA, Kirschner LS, Nguyen T, Carney JA, Oldfield EH (2000) Neurosurgical implications of Carney complex. J Neurosurg 92 (3):413–418
24. Raff SB, Carney JA, Krugman D, Doppman JL, Stratakis CA (2000) Prolactin secretion abnormalities in patients with the "syndrome of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas" (Carney complex). J Pediatr Endocrinol Metab 13(4):373–379
25. Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA, Shawker T (1997) Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). J Clin Endocrinol Metab 82(7):2037–2043
26. Ezzat S, Sarti DA, Cain DR, Braunstein GD (1994) Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 154(16):1838–1840

27. Mortensen J, Woolner LB, Bennett WA (1955) Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab 15(10):1270–1280
28. Garcia CJ, Daneman A, Thorner P, Daneman D (1992) Sonography of multinodular thyroid gland in children and adolescents. Am J Dis Child 146(7):811–816
29. Cetta F (1997) Familial nonmedullary thyroid carcinomas: a heterogeneous syndrome with different natural history and variable long-term prognosis. J Clin Endocrinol Metab 82(12):4274–4275
30. Stratakis CA, Kirschner LS (1998) Clinical and genetic analysis of primary bilateral adrenal diseases (micro- and macronodular disease) leading to Cushing syndrome. Horm Metab Res 30(6–7):456–463
31. Shenoy BV, Carpenter PC, Carney JA (1984) Bilateral primary pigmented nodular adrenocortical disease. Rare cause of the Cushing syndrome. Am J Surg Pathol 8(5):335–344
32. Stratakis CA, Sarlis N, Kirschner LS, Carney JA, Doppman JL, Nieman LK, Chrousos GP, Papanicolaou DA (1999) Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease. Ann Intern Med 131(8):585–591
33. Grant CS, Carney JA, Carpenter PC, van Heerden JA (1986) Primary pigmented nodular adrenocortical disease: diagnosis and management. Surgery 100(6):1178–1184
34. Sarkar R, Thompson NW, McLeod MK (1990) The role of adrenalectomy in Cushing's syndrome. Surgery 108(6):1079–1084
35. Doppman JL, Travis WD, Nieman L, Miller DL, Chrousos GP, Gomez MT, Cutler GB Jr, Loriaux DL, Norton JA (1989) Cushing syndrome due to primary pigmented nodular adrenocortical disease: findings at CT and MR imaging. Radiology 172(2):415–420
36. Carney JA, Toorkey BC (1991) Myxoid fibroadenoma and allied conditions (myxomatosis) of the breast. A heritable disorder with special associations including cardiac and cutaneous myxomas. Am J Surg Pathol 15(8):713–721
37. Carney JA, Toorkey BC (1991) Ductal adenoma of the breast with tubular features. A probable component of the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas. Am J Surg Pathol 15(8):722–731
38. Courcoutsakis NA, Chow CK, Shawker TH, Carney JA, Stratakis CA (1997) Syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex): breast imaging findings. Radiology 205(1):221–227
39. Azzopardi JG, Salm R (1984) Ductal adenoma of the breast: a lesion which can mimic carcinoma. J Pathol 144(1):15–23
40. Washecka R, Dresner MI, Honda SA (2002) Testicular tumors in Carney's complex. J Urol 167(3):1299–1302
41. Wieacker P, Stratakis CA, Horvath A, Klose S, Nickel I, Buhtz P, Muschke P (2007) Male infertility as a component of Carney complex. Andrologia 39(5):196–197
42. Stratakis CA, Papageorgiou T, Premkumar A, Pack S, Kirschner LS, Taymans SE, Zhuang Z, Oelkers WH, Carney JA (2000) Ovarian lesions in Carney complex: clinical genetics and possible predisposition to malignancy. J Clin Endocrinol Metab 85 (11):4359–4366
43. Crayford TJ, Campbell S, Bourne TH, Rawson HJ, Collins WP (2000) Benign ovarian cysts and ovarian cancer: a cohort study with implications for screening. Lancet 355(9209):1060–1063
44. Papageorgiou T, Stratakis CA (2002) Ovarian tumors associated with multiple endocrine neoplasias and related syndromes (Carney complex, Peutz-Jeghers syndrome, von Hippel-Lindau disease, Cowden's disease). Int J Gynecol Cancer 12(4):337–347
45. Carney JA (1990) Psammomatous melanotic schwannoma. A distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome. Am J Surg Pathol 14 (3):206–222
46. Utiger CA, Headington JT (1993) Psammomatous melanotic schwannoma. A new cutaneous marker for Carney's complex. Arch Dermatol 129(2):202–204
47. Siegal GP (2001) Osteochondromyxoma of bone: a lot more than fodder for the spelling-challenged. Am J Surg Pathol 25(2):268
48. Carney JA, Boccon-Gibod L, Jarka DE, Tanaka Y, Swee RG, Unni KK, Stratakis CA (2001) Osteochondromyxoma of bone: a congenital tumor associated with lentigines and other unusual disorders. Am J Surg Pathol 25(2):164–176