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 adrenocorticotropic 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 carcinomas). 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 (PMS) 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

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]. Notewor-thy, 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 (RIα) 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 PRKARIA 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 pigmnetations (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 dermal-epidermis junction), cafe-au-lait spots and atypical blue or compound nevi. Many patients present with a combination of the aforementioned skin lesions.

Spotty skin pigmnetations

Clinical features

Spotty skin pigmnetations are the most common clinical manifestation among CNC patients. The number of pigmented lesions ranges from few to myriad [1, 5, 10]. The pigmentation 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 periorcular and periorial 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 pigmnetations 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.
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

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

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)* |
| • Cardiac myxoma* |
| • Breast myxomatosis* or fat-suppressed MRI findings suggestive of this diagnosis |
| • PPNAD* or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle’s test |
| • Acromegaly due to GH-producing adenoma* |
| • LCCSCT* or characteristic calcification on testicular ultrasonography |
| • Thyroid carcinoma (at any age)* or multiple, hypoechoic nodules on thyroid ultrasonography in a prepubertal child |
| • Psammomatous melanotic schwannoma* |
| • Blue nevus, epithelioid blue nevus (multiple)* |
| • Breast ductal adenoma (multiple)* |
| • Osteochondromyxoma |

Supplemental criteria:

1. Affected first-degree relative
2. Inactivating mutation of the PRKAR1A gene

In 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

In 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
papules, to large (up to 5 cm) pedunculated 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. 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

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

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**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).

**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).
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].

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.
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 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].

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)

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

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].

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].
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].
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].
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...
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.

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