Review Article

Osteochondromyxoma: Review of a rare carney complex criterion

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1. Introduction

Carney complex (CNC) is a rare, autosomal dominant, genetically heterogeneous familial multiple endocrine neoplasia and lentigiosis syndrome that affects a number of organs [1–5]. First described in 1985 by J. Aidan Carney as the combination of myxomas, spotty pigmentation and endocrine overactivity, it has since been further characterized by osteochondromyxomas, recurrent cardiac myxomas (the lethal component of CNC), cutaneous and bilateral breast myxomas, multiple endocrine neoplasms, psammomatosus melanotic schwannomas, pigmented mucosal and skin lesions, large-cell calcifying Sertoli cell tumors, growth hormone-secreting pituitary adenomas, and breast ductal adenomas [2,6–10]. Diagnosis is based on the presence of at least two of these clinical criteria, confirmed by histology or one criterion and either a first-degree family history of CNC or a PRKAR1A mutation (HGNC:9388) [3,6]. Carney complex (OMIM 160980) is distinct from Carney triad (OMIM 604287) and Carney-Stratakis syndrome (OMIM 606864) although all three are related to their eponym, Professor Emeritus of Pathology, J. Aidan Carney, MD, PhD. The term Carney complex was designated by Bain, which included nearly all the prior acronym syndrome patients with LAMB (lentigines, atrial myxoma, and blue nevi) and NAME (nevi, atrial myxoma, myxoid neurofibromas, and ephelides) [11,12]. CNC also has similarities to other syndromes including Bannayan, Cowden, and McCune-Albright syndromes [4].

As of 2013, more than 750 cases of Carney complex have been reported worldwide [13]. Given this rarity, referral of patients to centers with expertise in CNC is advised [1]. It is therefore beneficial for all providers to be aware of CNC criteria to identify patients with possible CNC for further evaluation. The most common presentation (> 75% of CNC) which is also a diagnostic criterion of CNC is spotty pigmented skin lesions which normally appear early in life [1,12,14,15]. These are most often lentigines and epheledhial blue nevi (with cafe-au-lait spots less classically observed), which can be found anywhere on the body but are typically on the face, particularly the vermilion lip borders, eyelids, conjunctiva, and external ear [9,16,17].

As opposed to the commonly found skin lesions, osteochondromyxoma (osteochondroma containing myxoid elements) is one of the least common presentations of CNC, yet also one of its 11 clinical diagnostic criteria. Osteochondromyxoma (OMX) of bone is an extremely rare tumor that is always associated with lentigines and other unusual disorders, and it has in fact been called “Carney bone tumor” since it is typically associated with Carney complex [18]. OMX is the most common CNC bone tumor, affecting about 1% of CNC patients (compared to primary pigmented nodular adrenocortical disease (PPNAD), the most common endocrine tumor in CNC, found in 60% of CNC patients) [19,20]. OMX originate from bony cortices and have been observed in the nasal region, as well as the tibia and radius [5]. OMX is the most recently described tumor associated with CNC and causes swelling, local inflammation, and discomfort with symptoms depending on its site and size [19,21]. Via imaging, OMX lesions are considered benign however a detailed imaging evaluation is recommended for patients with any CNC findings because of its potential lethality [2,22]. Although OMX is a rare manifestation of CNC it is important to identify since symptoms of skeletal neoplasm are nonspecific, often leading to...
an erroneous diagnosis especially since primary bone tumors in early childhood are uncommon [23]. As recently as 2006 OMX was identified as an ‘unresolved question’ due to a lack of literature on the topic [24]. This review covers the current understanding of OMX by characterizing its presentation, pathology, genetics, management and prognosis.

2. Presentation

Osteochondromyxoma can occur at any age, but typically presents before age 2 and has been reported at birth [1,5,25]. Carney et al. hypothesize that the tumor itself can be congenital [5]. Though little has been published on the appearance of OMX, it can be distinguished based on its unique site, symptoms, and radiographic appearance from other craniofacial myxoid bone lesions (e.g. chondroblastoma, chondromyxoid fibroma, rhabdomyosarcoma, myxoid chondrosarcoma, and neurofibroma) [26,27]. OMX can occur in any bone but most frequently presents on the diaphysis of long bones (especially the tibia and radius) as well as the sinus and nasal bones [2,5,16,21,27–29]. Two cases have reported occlusion of the nasal sinus due to an OMX tumor [5,18]. If not surrounding vital structures, the mass may go unnoticed until becoming large in size. Such a case was reported from a tumor growing on the tibia [5]. Other historical cases, all in the non-English literature, have reported OMX of the rib, chest wall, and spine [30–32].

Osteochondromyxoma is characterized as a painless mass with additional symptoms due to edema and mass effect [5,7,27,29]. One case, for example, involved an infant with a tumor blocking the nasal turbinates, which led to difficulties with breastfeeding [5]. Since OMX is associated with 1% of patients with Carney complex, other symptoms pertaining to CNC may present, namely cardiovascular and endocrine abnormalities along with spotty skin pigmentation [28,29,33]. While OMX in young patients is associated with Carney complex, OMX in adults can occur as an isolated entity [5]. For example, a 2009 case reported OMX of the maxilla in a 21-year-old woman who did not exhibit any other Carney complex criteria [18].

Although OMX is a benign neoplasm it can exhibit locally invasive characteristics similar to that of the most common primary bone tumor, osteosarcoma [34]. Xenotransplantation of affected tissue into mice models has shown tumor presence and growth in as few as eight weeks. Although local growth is rapid and invasive, it has not been shown to metastasize [25,28]. Although similar to osteosarcomas, this pattern has also been exhibited by normal parathyroid cells with orthotopic autotransplantation and xenotransplantation in mice models [35,36].

On imaging OMX is well circumscribed and can be destructive and mineralized, with other aspects of its appearance varying depending on the tumor’s location [27]. The mass can show expansion of the affected bone area with mixtures of lucent and sclerotic regions. On MRI (the most precise imaging method for symptomatic bone masses), OMX found on the spine presents with increased T2-weighted signaling. Imaging differential diagnosis includes chondromyxoid fibroma, mesenchymal hamartoma, myxoma, chondrosarcoma with myxoid change, and fibrocartilaginous mesenchymoma [7,19].

3. Pathological features

Gross pathology may present a well-circumscribed, bony or cartilaginous, calcified, white mass. The mass tends to change the nature and matrix of the surrounding bone structures, but it also may stay confined within the periosteme. The tumor erodes surrounding bone and invades soft tissue. Encapsulation is seldom present, but has been reported. Histologically, capsules are marked with 10–15 cell-thick parallel layers; cells contain eosinophilic cytoplasm and nuclei arranged in rows. However, if no capsule is appreciated, histological inspection shows no well-defined border between the tumor and surrounding normal tissue; signs of inflammation are seldom noted [5]. Histology consists of sheets with lobular areas, polymorphic cells, chondroid, osteoid, and hyaline bands [27]. There is histological similarity between OMX and bizarre parosteal osteochondromatous proliferation (BPOP), also known by its eponym Nora’s lesion, first reported in 1983), another rare, locally aggressive, benign condition; however, on H&E OMX lacks the blue staining of immature bony trabeculae found with BPOP [37,38].

Light microscopy yields varying findings. However, the tumor is usually composed of a mixture of mesenchymal cells, basophilic myxoid material, and mucopolysaccharide ground substance. The degree of cellularity is inversely proportional to the amount of myxoid material and matrix [5,25]. Osteoid and bone, immature and mature cartilage, hyaline fibrous bands and nodules, and collagen fibers are also scattered within the tumor, varying throughout the tissue sample. While the cells are usually organized in sheets in either well-defined or disorganized microlobular or macrolobular patterns, there are occasional ill-defined cell whorls. Larger lobules are confined by a peripheral cellular border, which also contain multiple small, sinusoidal blood vessels. With accumulation of the matrix, the sheets of cells tend to undergo dissociation from small and irregular shaped cell aggregates to tenuously-linked strands and cords that form a reticular network of cells [5]. Atypical cellularity and necrosis are seldom seen [4,5,25].

Most cells found in microscopy are polygonal, stellate, and bipolar. Cytoplasmic vacuolization with occasional inclusion bodies are common around myxochondroid areas. Chondroblast-like cells and osteoblast-like cells are found throughout the tissue; both cells are involved with osteoid development. Small foci containing adipocytes are found throughout samples. The nuclei of cells are rarely atypical. They present as well preserved, chromatic, and vesicular with small, discernable nucleoli [5].

Histochemically, the cytoplasm of tumor cells stain periodic acid-Schiff (PAS) positive. The positivity is strongest where matrix is minimal, as suggested by the inverse proportion of cell to matrix. Cell cytoplasm and matrix are positive for colloidal iron. Tumor cells stain positive for vimentin and occasionally S-100 protein. Collagen II staining is focal and moderate while collagen IV staining is minimal. Movat pentachrome staining helps discern the tumor components: myxomatous (faint blue), cartilaginous (blue, green, and olive), hyaline (yellow), and osseous (yellow, scarlet, and brick red) [5].

4. Genetics

The American College of Medical Genetics and Genomics as well as the National Society of Genetic Counselors recommend genetic counseling for cancer predisposition when a patient with Carney complex presents with OMX [39]. So far two loci have been associated with Carney complex: one in chromosome 2 and the other in chromosome 17; and in inherited cases, Carney complex is an autosomal-dominant trait with almost 100% penetrance [1,10,33,40]. It is most often associated with mutations (most often deletions) in 17q24 in the gene PRKAR1A (protein kinase cAMP-dependent type 1 regulatory subunit alpha, HGNC:9388), also known as CNC1, as well as in 2q31 in the gene PDE11A (phosphodiesterase 11A, HGNC:8773), with ongoing research to identify other genes [9,40–42].
About 1% of Carney complex patients exhibit osteochondromyxoma [1,29]. It is believed to arise from distorted mesenchymal stem cells designated to become osteoblasts [4,25]. In particular, the mutation is seen to cause a hyperstimulation of protein kinase A (PKA) when elevated levels of cyclic AMP (cAMP) are present within the cell [4]. Carney complex has a mutation affecting the sensitivity and function of the alpha-1 subunit of protein PKA toward cAMP [1,33]. Parathyroid hormone (PTH) stimulates osteoblasts via the PKA/cAMP pathway. Since the genetic mutation causes hyperresponsiveness to elevated levels of cAMP, it is believed that PTH serves as a chronic stimulator for tumor growth [43,44].

In mice experiments of the Prkar1a mutation (MGI:104878) seen in Carney complex, Kirschner et al. found that mice sustaining the Prkar1aΔ2δ+ mutation exhibited multiple tumors on the tail that were described as similar to OMX human lesions. The tumors arose in 50% of mice with the mutation in eight months and in 80% at one year. Radiographs showed radiolucent lesions in the vicinity of the tailbone [4]. This radiographic appearance mimics that of OMX in humans; the tumor replaces the trabecular network seen in normal bone into myxoid and gelatinous features [5]. Histologically, the tumors of the mice tails showed a mixture of spindle, polygonal, stellate, and inflammatory cells within a background of matrix. These characteristics are similarly described in osteochondromyxoma lesions found in Carney complex patients [4,5].

Microarray analysis of mutated osteoblasts shows about 250 altered transcripts. One of them is Runx2 (Runx-transcription factor-2, MGI:99829), a gene that is claimed to be a major control for osteoblast differentiation [25,45,46]. Chromatin immunoprecipitation and luciferase assays also show repression of DNA binding and functioning of Runx2 at its target genes. There are also reductions in Runx2-cooperating transcription factors such as Foxo1 (forkhead box O1, MGI:1890077) and Atf4 (activating transcription factor 4, MGI:88096) [46]. The osteoblasts affected by the Prkar1a mutation also display suppressed bone nodule formation in addition to markers osteocalcin and osteopontin [25,46]. Downregulation of other markers includes Il6st (interleukin-6 signal transducer, MGI:96560), a gene that codes for gp130 subunit of the IL-6 receptor [47]. However, the transcript with the most significant drop is CILP (cartilage intermediate layer protein, MGI:2444507), a structural protein that plays a role in matrix composition and bone formation [48,49].

One gene noted to be upregulated via evidence of increased mRNA and protein levels is Wnt5a (Wingless-Type MMTV Integration Site Family, Member 5A, MGI:98958). Wnt signaling is known to aid in bone formation by in

pathology are similar in the two syndromes, histological appearances differ. The mice exhibiting the Prkar1aΔ2δ+ mutation contained hypocellular and immensely myxoid matrixes. The bony trabeculae also were rimmed with normal-appearing osteoblasts. These findings are similar to Carney complex patients with osteochondromyxoma. Polysostotic fibrous dysplasia in MAS contain greater cellularity and lack a normal-osteoblast comprised rim [4,50].

5. Management and prognosis

With complete excision OMX has a good prognosis (unlike several other bone myxoid lesions, e.g., chordomyoid fibroma and rhabdomyosarcoma) [27]. In fact, complete excision of OMX can be curative, however local recurrence is very common with incomplete resection [5,27,34]. Disease recurrence is therefore more likely at sites where complete resection is difficult [28]. Since metastasis have never been suggested, recognition and complete excision are key to a good prognosis [4,5,25].

Conflict of interest statement

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Human and animal rights and informed consent

This review article does not contain any studies performed by any of the authors on human or animal subjects.

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