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Original Article

Abnormal karyotypes in osteochondroma: Case series and literature review

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ABSTRACT

Background: Osteochondroma is the most common benign bone tumor. However, there are infrequent studies karyotyping solitary osteochondromas.

Methods: Retrospective review of the University of California, Los Angeles pathology database was performed for karyotype analyses ($N = 522$ specimens).

Results: Two previously undescribed karyotypes were identified. First, was a karyotype showing paracentric inversion of chromosome 7. Second, was a karyotype showing monosomy 3, 6 and 13.

Conclusions: Abnormal karyotypes may be more frequently encountered in osteochondroma than previously understood. However, the clinical significance of these abnormalities are yet unknown.

1. Introduction

Osteochondroma is a benign bony protrusion covered by a cartilaginous cap, commonly involving the long bones. Osteochondroma is the most common bone tumor, with an estimated incidence of 35% of benign bone tumors and 8% of all bone tumors, although these numbers may be an underestimate.[1] Osteochondromas, although benign, can cause significant local symptoms in a minority of cases including nerve impingement, mechanical obstruction, pseudoaneurysm of adjacent vessels, and infarction or fracture of the tumor itself. Osteochondromas have been identified in skeletons dated as far back as 11th century Croatia,[2] 2nd century Poland,[3] and even 3rd century BC Britain.[4] Despite their historical and current day prevalence, accompanying morbidity and potential for malignant transformation, the underlying biology and etiogenesis of osteochondromas is still poorly understood.

Osteochondromas may occur as either sporadic solitary lesions or as multiple lesions as part the autosomal dominant, hereditary multiple exosostes (HME).[5,6] The histologic appearance of sporadic or multiple/hereditary osteochondromas is identical. The genetic loci for HME have been identified (all of which are also involved in sporadic osteochondroma): 8q24.1 (*EXT1*), 11p11~12 (*EXT2*), and 19p (*EXT3*).[7–9] The identification of EXT1-3 polymerase mutations have made it clear that

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osteochondromas represent true cartilaginous tumors, rather than developmental malformations.

Collectively, there has been little interest in the cytogenetic characterization of sporadic osteochondromas, and karyotypes are not routinely obtained in solitary osteochondromas. Bridge et al, described the karyotype of 34 osteochondroma specimens of which 29% showed clonal karyotypic abnormalities.[10] Feely et al later expanded this dataset to describe the karyotype of 37 osteochondroma specimens of which up to 51% showed either random or clonal karyotypic abnormalities.[11] The most frequent chromosomes involved were chromosomes 8, 6 and 12 in descending order of frequency. The majority of chromosome 8 abnormalities involved loss or rearrangement of 8q24.1 (*EXT1*), and chromosome 11 abnormalities typically involved 11p11-12 (*EXT2*).[10] However, not all osteochondromas have detectable EXT mutations. For example, Bridge et al found 8q22-24 (EXT1) aberrations in only 33% of specimens examined, while Feely et al found 8q24.1 loss by FISH in 79% of cases.[10,11] In aggregate, these data suggest that EXT mutations are the main associated cytogenetic alteration in osteochondroma, but also that other, as yet unknown, cytogenetic aberrations may also predispose for the formation or growth of osteochondroma.

Other chromosomal aberrations have been identified in osteochondromas. For example, several other breakage points include 12q13, 2p21, 6p25 and 3q27.[10] Of these, 12q13-15 is found in both benign and malignant cartilage neoplasms and localizes to the major component of cartilage matrix, Type II collagen.[10,12] However, it is clear that in general benign cartilage tumors have less complex karyotypes than their malignant counterpart (chondrosarcoma).[11] Thus, there are multiple cytogenetic aberrations that accompany, and possibly incite, formation of osteochondroma. Undoubtedly, the continued study of sporadic osteochondromas will find of cytogenetic aberrations of biological relevance to improve our understanding of this common bone tumor.

To this end, we examined our pathology database of 522 osteochondromas to identify any previously undocumented cytogenetic abnormalities. Our hypothesis was that as yet unidentified cytogenetic aberrations may be present in our database of specimens, and that identification of new chromosomal changes may yield profitable future insight into the genetic bases for this common tumor.

2. Materials and methods

2.1. *Database search*

Computerized search of the University of California, Los Angeles (UCLA) pathology database from 2000 to 2012 was performed for any karyotype analysis, using the search terms 'osteochondroma(s), exostosis(es). Clinical data was obtained including patient age, gender, and pertinent medical, surgical, radiographic and pathologic records.

2.2. *Chromosome analysis*

A G-banded chromosome study was performed using standard cytogenetic techniques. Briefly, two unstimulated cultures were set up in RPMI 1640 medium enriched with 20% fetal calf serum, giant cell tumor conditioning media, L-glutamine, and antibiotics (penicillin and streptomycin). The cells were cultured for 24 and 48 h in a humidified environment with 5% CO2 in a 37°C incubator until harvest.

Before harvesting, the cultures were treated with Colcemid (25 mL) for 16e18 h. Soon after, the cells were exposed to hypotonic solution (0.075 mol/L KCl) and fixed with methanol/acetic acid (3:1). The slides were prepared and stained using a G-banding (Trypsin-Giemsa-Wright) technique. Up to twenty metaphases were analyzed and karyograms were prepared using the CytoVision computer assisted karyotyping system (Applied Imaging, Santa Clara, CA, USA). The karyotypes were described according to the International System for Human Cytogenetics Nomenclature.[13]

3. Results

Karyotypes were infrequently ordered for osteochondroma (3/522 patients, 0.57%) in records dating back 12 years. Of these, two abnormal karyotypes were identified. The first was a 22 year old, otherwise well female with an asymptomatic, palpable right rib mass noticed for 3 weeks duration. No personal or family history of bone tumors was elicited. Computerized tomography (CT) of the chest demonstrated an expansile, partially ossified, 3.4 cm mass arising from the anterolateral aspect of the right first rib (Fig. 1a,b). Bone scan showed intense hypermetabolic focus in the area of the mass, with no significant uptake elsewhere. Biopsy showed hypocellular lobular cartilage adjacent to trabecular bone with marrow elements, suggestive of osteochondroma. Surgical excision was performed, showing a large, pedunculated lesion arising from the resected rib (Fig. 1c). Histological analysis of the resection specimen showed hypocellular lobular cartilage with overlying periosteal fibrous tissue, and with underlying endochondral ossification, and trabecular bone with bone marrow (Fig. 1d), confirming the diagnosis of osteochondroma. No cytologic atypia was observed. Karyotyping was performed from biopsy tissue as the size of the lesion was concerning for malignancy. Karyotyping demonstrated monosomy of chromosomes 3, 6 and 13, additional material of unknown origin on 4q28 and 3 marker chromosomes in all metaphase cells examined. The karyotype was described as: 46,XX,-3,add(4)(q28),-6,-13,+3mar[10] (Fig. 1e).

The second patient was an otherwise well, 37-year-old female who presented with a palpable mass noticed over her left knee for the past 8 months. No personal or family history of bone tumors was elicited. CT of the leg demonstrated a well corticated, 2 cm osseous protrusion along the anteromedial aspect of the tibial tubercle, with medullary and cortical continuity with the underlying bone (Fig. 2a). Surgical excision was performed, and the resection specimen was received in fragments. As malignancy could not be excluded, karyotyping was performed as well as routine processing for histology. Based on the typical histologic appearance, a pathologic diagnosis of osteochondroma was rendered (Fig. 2b,c). Typical findings of osteochondroma were appreciated, including low-grade cartilage, with an outer fibrous periosteum, and underlying bone with marrow cavity. No cytologic atypia was