Solid Tumour Section
Review

Bone tumors: an overview

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Identity

Note

Primary skeletal neoplasms account for 0,2% of human tumors, whereas involvement of skeletal tissue by metastatic disease is much more common. Their soft tissue-related counterparts outnumber bone tumors by a margin of approximately 10:1. Because of their rarity, not much is known about the etiology and risk factors of bone tumors, although a difference in ethnical distribution has been observed.

Bone tumors are mostly of mesenchymal origin, though for example Ewing sarcoma is thought to have neuroectodermal precursor cells. Classification of the World Health Organization will be followed in this overview. Grading of bone tumors is roughly based on the cellularity of the lesion compared to the amount of extracellulair matrix, nuclear features, the presence of mitotic figures and necrosis. Staging via the TNM system is normally not used, because metastases in lymph nodes are not frequent in these lesions. Therefore staging is based on degree of differentiation of the tumor tissue and local and distant spread of the tumor. Genetic information and references are provided for tumors investigated in more than a single case.

Classification

Cartilage tumors
Osteochondroma
Chondromas
Enchondroma
Periosteal chondroma
Chondroblastoma
Chondromyxoid fibroma
Chondrosarcoma
Dedifferentiated
Mesenchymal
Clear cell
Periosteal
Osteogenic tumors
Osteoid osteoma
Osteoblastoma
Osteosarcoma
Conventional
Teleangiectatic
Small cell
Low grade central
Secondary
Parosteal
Periosteal
High grade surface
Fibrogenic tumors
Desmoplastic fibroma of bone
Fibrosarcoma of bone
Fibrohistiocytic tumors
Histiocytoma of bone
Ewing sarcoma/Primitive neuroectodermal tumor
Giant cell tumors
Giant cell tumor
Notochordal tumors
Chordoma
Vascular tumors
Haemangioma and related lesions
Angiosarcoma
Myogenic, lipogenic, neural and epithelial tumors
Leiomyosarcoma of bone
Lipoma of bone
Adamantinoma and osteofibrous dysplasia
Tumors of undefined neoplastic nature
Aneurysmal bone cyst
Simple bone cyst
Fibrous dysplasia
Langerhans cell histiocytosis (LCH)

Clinics and pathology

Cartilage tumors

Osteochondroma

Germ line mutations in the tumorsupressor genes Exostosin-1 (EXT-1) located at 8q24 and Exostosin-2 (EXT-2) located at 11p11-p12 have been found in hereditary multiple osteochondromas (MO). Somatic mutations are extremely rare in these tumors. In four tumors aberrations involving the region 1p13-p22 were shown.

Chondromas

- Enchondroma

By conventional cytogenetic analysis, abnormalities involving chromosome 6 and the long arm of chromosome 12 have been detected.

- Periosteal chondroma

This subtype has not been individually investigated.

Chondroblastoma

Although a dozen of case reports have been published, no specific alterations were found in these rare benign tumors.

Chondromyxoid fibroma

Structural rearrangements of chromosome 6 are found to be non-random, particularly involving the long arm (q13 and q25) and p25 on the short arm.

Chondrosarcoma

In most genetic studies no difference is made between peripheral, central chondrosarcoma and other subtypes. CGH revealed extensive genetic aberrations; gains of whole chromosomes or chromosome arms at 20q (32-38%), 20p (24-31%), and 14q23-qter (24-28%).

In a comparative study, 19 of 20 peripheral chondrosarcoma showed LOH at the loci for EXT, EXTL, 13q14, 17p14, 17p13, 9p21 and chromosome 10, while only 3 of 12 central chondrosarcoma did. In addition the ploidy status in peripheral chondrosarcoma showed wide variation (0,56-2,01), whereas central chondrosarcomas were predominantly periploid.

- Dedifferentiated

In the cartilaginous, as well as in the dedifferentiated part of the tumor an identical somatic 6 bp deletion in exon 7 of p53 and loss of the same copy on chromosome 13 had been found. These findings provide evidence for a common origin of both parts.

- Mesenchymal

A Robertsonian (13; 21) translocation, der(13;21)(q10;q10), was detected in two cases, together with loss of material from chromosome 8 and 20 and gain of material from chromosome 8.

- Clear cell

No specific alterations have been reported.

- Periosteal

No specific alterations have been reported.

Osteogenic tumors

Osteoid osteoma

Involvement of band 22q13 and loss of the distal part of arm 17q were detected in two out of three analyzed cases.

Osteoblastoma

No consistent aberrations have been detected in four cases, although clues are leading to deregulation of the cell cycle. No telomerase activity could be found.

Osteosarcoma

- Conventional

Although most osteosarcomas reveal complex chromosomal aberrations, no specific alterations have been found. Amplification at 1q21-23 and 17p, together with co-amplification of 12q13-15 are frequently reported. In 14-27% of osteosarcomas, the MDM2 gene is amplified and in 41% the PRIM1 gene. Amplification of the CDK4 gene is found in aggressive lesions. Chromosome 12p is differently amplified in low- versus high-grade osteosarcomas. The MYC gene has been shown to be amplified in 44% of osteosarcoma (8q24).

- Teleangiectatic

In contrast to the conventional osteosarcomas, no amplifications were detected in four cases. Complex chromosomal changes were found.

- Small cell

No genetic alterations have been reported on this subtype of osteosarcoma.

- Low grade central

The complex aberrations found in high-grade osteosarcomas could not be identified in these low-grade variants. Recurrent gains have been reported with minimal common regions at 12q13-14, 12p and 6p21.

- Secondary

In tumors developing in bone after radiation, chromosomal losses are more frequently observed than gains. Especially 1p, which is lost in 3% of the conventional type, is lost in 57% of the radiation-associated type.

In osteosarcomas secondary to Paget Disease of Bone (PDB) LOH is found at 18q, the locus for PDB.

- Parosteal

Ring chromosomes are reported as the sole alteration in parosteal osteosarcoma. Using FISH techniques, the SAS, CDK4 and MDM2 genes are shown to be co-amplified with a minimal common region at 12q13-15 in the ring chromosomes.

- Periosteal

Complex chromosomal aberrations were reported.

- High grade surface
These lesions have not been studied as a specific subtype.

Fibrogenic tumors

Desmoplastic fibroma of bone
Like in desmoid tumors, trisomies 8 and 20 are commonly found.

Fibrosarcoma of bone
No cytogenetic investigations on fibrosarcoma have been published.

Fibrohistiocytic tumors

Histiocytoma of bone
Of the benign form of this tumor, no cytogenetic information is available. Its malignant counterpart shows LOH at chromosome 9p21-22, which has also been shown by CGH before.

Ewing sarcoma/Primitive neuroectodermal tumor

The most common rearrangement (85%) in this tumor is translocation t(11;22)(q24;q12). Consequently, this leads to the fusion protein EWS/FLI1. Other translocations found in the Ewing Sarcoma gene are listed below:

Fusion of	to	translocation	%
EWS	FLI1	t(11;22)(q24;q12)	85
EWS	ERG	t(21;22)(q22;q12)	10-15
EWS	ETV1	t(7;22)(p22;q12)	< 1
EWS	FEV	t(2;22)(q36;q12)	< 1
EWS	E1AF	t(17;22)(q21;q12)	< 1

Giant cell tumors

Reduction in length of the telomeres, as well as telomeric association, has been demonstrated in these tumors. Most commonly 11p, 13p, 14p, 15p, 19q, 20q and 21p are affected.

Notochordal tumors

Chordoma
Nine of sixteen investigated chordomas were hypodiploid with a chromosome number ranging from 33 to 44. Chromosomes 3, 4, 10, and 13 are most commonly lost, and in half of the cases the following segments are lost up to the telomere: 1p31, 3p21, 3q21, 9p24, 17q11. Because LOH is found at band 1p36, a tumor suppressor gene is thought to exist on distal 1p.

Vascular tumors

Haemangioma and related lesions
No cytogenetic investigations reported.

Angiosarcoma
An identical translocation of chromosomes 1 and 3 has been reported in two epithelioid haemangioendotheliomas.

Myogenic, lipogenic, neural and epithelial tumors

Leiomyosarcoma of bone
5 Grade IIB tumors demonstrated a rate of genomic loss of 90%, whereas high micro satellite instability was not observed. Allelotyping revealed loss of pRb in the tumors. In addition, chromosomal loss was noticed in human telomerase subunit-linked markers.

Lipoma of bone
Only one case study is published about the benign form of this tumor. On its malignant counterpart, liposarcoma of bone, no genetic information has been published.

Adamantinoma and osteofibrous dysplasia
Cumulating evidence indicates that classic adamantinomas derive from their osteofibrous dysplasia (OFD)-like counterparts. OFD and adamantinoma show common cytogenetic abnormalities. In 15 cases of adamantinoma (n=11) and OFD (n=4) trisomies of chromosomes 7, 8, 12, 19 and 21 were detected. These findings further substantiate the clonal origin of OFD and the common histogenesis of OFD and adamantinoma.

Tumors of undefined neoplastic nature

Aneurysmal bone cyst
Aneurysmal bone cysts can be primary or secondary to other bone lesions. Chromosome bands 16q22 and/or 17p13 (USP6 gene) are non-randomly rearranged in ABC, regardless of tumor type (classic and solid) and of location (osseous and extraosseous). However, rearrangements are absent in secondary ABC. A recurrent t(16;17)(q22;p13) has been identified, but other chromosomal segments as translocation partner for each chromosome have been described.

Simple bone cyst
Only one case report describes structural rearrangements.

Fibrous dysplasia
Two fibrous dysplasia cases exhibited either a completely normal karyotype or single cell aberrations. Evidence that this lesion is neoplastic comes from the fact that clonal chromosomal aberrations have been found. In monostotic as well as polyostotic lesions activating GNAS1(20q13.2) mutations, known from the McCune-Albright syndrome, have been demonstrated.

Langerhans cell histiocytosis (LCH)
Studies of X-chromosome inactivation demonstrated that LCH is clonal.

Congenital and inherited syndromes

Beckwith-Wiedemann syndrome

This syndrome, which is caused by heterogenic genetic changes on 11q15, is subject to genomic imprinting. 3 Beckwith-Wiedemann syndrome chromosome regions (BWSCR) have been identified: BWSC1 near INS/IGF2, BWSC2 5 Mb proximal to BWSC1, and BWSC3 2 Mb even more proximal.

Enchondromatosis: Ollier disease and Maffucci syndrome

These syndromes are non-hereditary although a case of familial clustering has been reported. Mutations in the PTH receptor 1 have been found in two cases, but these results could not be confirmed in a larger series of 31 patients, suggesting that PTHR1 is not the culprit for enchondromatosis.

McCune-Albright syndrome

Mutations in the GNAS1 gene, located on 20q13, change the structure of the G-protein a-stimulatory subunit. Dysfunctions of the heterotrimeric G-protein complexes lead to this non-familial occurring disorder.

Multiple osteochondromatosis (MO)/Hereditary Multiple Exostosis

Mutations in one of the two exostosin (EXT) genes are responsible for this autosomal dominant syndrome. EXT1 is located at 8q24 and EXT2 at 11p11-p12. Most mutations are either nonsense, frame shift or splice-site mutations, leading to premature termination of the EXT proteins. This causes alteration of the gene products, which are functioning in the endoplasmatic reticulum as transmembrane glycoproteins, and will affect the biosynthesis of heparan sulphate proteoglycans, leading to altered growth factor signaling.

Familial Paget Disease of Bone

Familial Paget Disease of Bone (PDB) demonstrates linkage to chromosome 18q. Some cases (PDB type 2) are caused by mutations in the TNFRSF11A gene on chromosome 18q22.1, which encodes RANK, a protein essential in osteoclast formation. The phenotype linked to chromosome 5q35 (PDB type 3) is caused by mutations in the SQSTM1 gene, the product of which is associated with the RANK pathway.

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