Bone: Osteosarcoma

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Identity

Note
Osteosarcoma is a malignant neoplasm of bone. It is among the most common non hematologic primary malignant tumors of bone in both children and adults. The conventional type arises in the intramedullary cavity of the bone and represents 75% of all osteosarcomas. These tumors penetrate and destroy the cortex of the bone and extend into surrounding soft tissues. In conventional intramedullary osteosarcoma, the predominant histologic pattern may be osteoblastic, fibroblastic, chondroblastic, giant cell rich, malignant fibrous histiocytoma like or partially telangiectatic.

Clinics and pathology

Epidemiology
The age of presentation of osteosarcoma occurs chiefly in two groups: 10 - 25 years of age, and more than 60 years of age. Osteosarcoma may arise as a de novo lesion or develop secondarily to a known premalignant lesion such as Paget disease, osteogenesis imperfecta, bone lesion, chronic osteomyelitis, fibrous dysplasia, giant cell tumor, osteoblastoma, or to a process such as radiation therapy. Several chemical agents such as beryllium oxide were shown to be inducers of osteosarcoma.

Some cases of osteosarcoma appear to be familial: in particular children with familial bilateral retinoblastoma have a incidence of osteosarcoma several hundred times that of an age-matched general population. This appears to represent both a genetic predisposition to de novo neoplasia and an increased susceptibility to radiation-induced sarcoma.

Patients with hereditary diseases such as Rothmund-Thomson syndrome, Bloom syndrome, and Li-Fraumeni syndrome were found to have increased risk of having osteosarcoma develop.

Clinics
Approximately 85% of patients with de novo osteosarcoma present before 20 years of age. More than 60% are in their second decade of life. Males are affected more often than females. Conventional osteosarcoma shows a marked predilection for the metaphyseal regions of the long bones. The distal femur accounts for one third of all cases, followed by proximal tibia, and the proximal humerus.
The most common presenting complaint is pain, usually from 1 to 8 months duration. Pathologic fractures are uncommon occurring in less than 5% of patients.
The classic radiographic finding is a large infiltrating metaphyseal lesion that arises in medullar bone and erodes through the cortex to from a large soft tissue mass. Osteosarcomas appear most often with a mixed lytic and sclerotic appearance.

Pathology
Osteosarcoma is composed of proliferating spindle-shaped cells that directly produce osteoid or immature bone (fig 1).
Approximately 75 % of osteosarcomas arise in the intramedullary cavity and are referred to as “classical” or “conventional” osteosarcoma (fig 2).
“Conventional” osteosarcomas can be divided into histological subtypes according to their predominant stromal differentiation: fibroblastic, telangiectatic and giant-cell rich.
Microscopic features: osteoblastic osteosarcoma with atypical cells elaborating immature osteoid.

Others types of osteosarcomas are:
- cortex-associated osteosarcomas,
- low grade (central) osteosarcomas,
- osteoblastoma-like osteosarcomas,
- disease-associated osteosarcomas,
- multicentric osteosarcomas,
- post-irradiation osteosarcomas.
- Osteosarcoma of the gnathic bones.

Most osteosarcomas are easily recognized based on their high-grade obviously anaplastic cells and uniquivocal osteoid production. The neoplastic cells in high grade conventional osteosarcomas have marked nuclear pleomorphism, conspicuous chromatin abnormalities, prominent nucleoli and many mitotic figures some of which are atypical. In the fibrosarcomatous pattern of osteosarcoma, the stroma is composed of spindle cells. Osteosarcomas may contain large areas that resemble malignant fibrous histiocytoma.

**Treatment**

Osteosarcoma is a chemosensitive tumor especially to high-dose methotrexate. The usual therapy is 8 to 12 weeks pre-operative chemotherapy, followed by conservative surgery or amputation, then by post-operative chemotherapy adapted to the histological response to pre-operative chemotherapy. But, 30 to 40% of patients have a bad histological response to pre-operative treatment and a worse long term prognosis.

**Prognosis**

Molecular events associated with disease aggressiveness and chemotherapy response may serve as prognostic factors. 

Age, localisation, tumoral mass, initial metastatic disease are prognostic factors. The most important predictor of outcome at diagnosis is the presence or absence of metastases. The most reliable prognostic factor is the histological response to pre-operative chemotherapy. Elevated expression of P-glycoprotein in immunochemistry was associated with a decreased probability of event-free survival. The expression of HER2/neu may be a predictor of chemotherapy response and prognosis in osteosarcoma. For some authors, it is correlated with a poor survival rate. 

At present, RB gene LOH (loss of heterozygosity) appears as an early predictive feature for primary osteosarcomas, indicating a possible unfavourable outcome whereas its absence is correlated with a favourable prognostic.

**Cytogenetics**

**Cytogenetics Morphological**

The majority of osteosarcomas are characterized by complex chromosomal abnormalities with pronounced cell-to-cell variation or heterogeneity. A high frequency of aneuploidy and numerous structural abnormalities has been described. 

High-grade tumors were seen to be hyperdiploid whereas low-grade tumors were seen to be diploid. 

Nevertheless some authors studied the association between the degree of aneuploidy and prognosis and response to chemotherapy. They reported that patients whose tumors showed a non diploid DNA content had a longer event-free survival after surgical resection and chemotherapy than did those with diploid tumors. The most commonly identified numeric chromosomal abnormalities were gain of chromosome 1 and loss of chromosomes 9, 10, 13 and 17. The chromosomal breakpoints most commonly involved in structural rearrangements include 1p11-13, 1q11-12, 1q21-22, 11p14-15, 14p11-13, 15p11-13, 17 p and 19q13.
Macroscopy aspect of an osteosarcoma: hemorrhagic and destructive tumor of the metaphysis of the right tibia. Bilateral rupture of cortical and invasion of epiphyseal plate.

**Cytogenetics Molecular**

Many studies were reported in osteosarcomas with comparative genomic hybridization (CGH). DNA sequence copy number increases have been identified on the regions 1q21, 3q26, 6p, 8q, 12q12-13, 14q24-qter, 17p11-12, Xp11.2-21 and Xq12. The most interesting of these abnormalities are copy number increase at 8q, 1q and 17p. Patients with copy number increases at 8q have a shorter survival, whereas patients with a copy number increase at 1q21 showed a longer survival. Amplicon, 17p was identified as in conventional cytogenetic and in CGH. Ring chromosomes, double minutes and homogeneously staining region are seen in some osteosarcomas. They signify the presence of gene amplification. Ring chromosomes frequently observed in paraosteal osteosarcomas, low-grade tumor, are associated with amplification of DNA at chromosome 12q13-15 in CGH technique. This region contains MDM2 and CDK4 genes.

**Genes involved and proteins**

**Note**

A number of important genes have been identified, including various tumor suppressor genes, oncogenes and genes coding for growth factors. Inactivation of both P53 and RB pathways appears to be a central event in the genesis of osteosarcoma.

**RB**

Alterations in the RB gene pathway:

- It is known that patients affected by hereditary RB have 1000 times the incidence of osteosarcoma compared with the general population. Sporadic osteosarcomas show alteration of the RB gene in 70% of cases.
- Loss of heterozygosity (LOH) at 13q, the site of gene RB is present in approximately 60% to 70% of osteosarcomas. And recently LOH at the RB locus has been proposed as a poor prognostic factor in osteosarcoma.
- Gross structural rearrangement of the RB gene is present in 30% of these tumors and point mutations in only 10%.
- Abnormalities of the RB gene are commonly seen in osteosarcoma but other components of the RB-pathway gene can be subject to genetics alterations: INK4, p16, CDK4 and cyclin D1. The INK4A gene located on chromosome 9p21 is inactivated in about 10% of osteosarcomas. Loss of p16 expression is also found in 10% to 15% of tumors and is correlated with decreased survival in pediatric osteosarcomas.
- Amplification of the 12q13-15 chromosomal region which contains both CDK4 and MDM2 is seen in about 10% of osteosarcomas.

**P53**

**Note**

Alterations in the P53 pathway:

Inactivation of the p53 pathway is central event in many tumors including osteosarcoma. The p53 gene is located on chromosome 17p13, chromosomal region frequently altered in cytogenetic analysis. Abnormalities of p53 were identified in 50% of cases. p53 mutations are more often missense type. Alterations of p53 observed in osteosarcoma can be allelic loss (75-80%) or gene rearrangements (10-20%) or point mutations (20-30%). In patients with the Li-Fraumeni syndrome who have a germline mutation of
p53 they are a high risk of osteosarcoma. And in 3% of patients with sporadic osteosarcoma, germline mutations in p53 are identified.

Some genes are involved in the regulation of p53 and abnormalities of these are detected in cases of osteosarcoma.

- The MDM2 gene located on chromosome 12q13 encodes a protein that negatively modulates p53 function by binding the p53 protein. MDM2 is amplified in 5-10% of osteosarcomas.

- Another important protein is the p14 product of the INK4A gene. The p14 protein exerts a protective effect on p53. For some authors either or two singular events: INK4A deletion or 12q13 amplification can inactivate two separate pathways of cell cycle control. But direct genetic alteration of both p53 and RB do not co-exist with either INK4A deletion or 12q13 amplification. So, three pathways of cell are possible to induction of an osteosarcoma.

**DCC**

**Note**

Others suppressor genes than RB and p53 can exist in osteosarcomas LOH have been describe on chromosomal region 3q26 and 18q22. On 18q22, is located DCC gene (deleted in colon cancer). Abnormalities of these regions are seen in Paget’s disease where osteosarcoma risk is increased.

**Note**

Some other oncogenes are known to be associated with osteosarcomas.

- C-fos is expressed in 61% of tumors. It was more frequently expressed in high-grade lesions and more often (42%) in patients who developed metastases.

- Likewise, c-myc is overexpressed in patients with metastatic osteosarcomas.

Her 2/neu is associated with 40% of tumors and decreased survival.

- SAS gene located on 12q13 is amplified in 36% of osteosarcomas and 100% of parosteal osteosarcomas. A possible mechanism linked to specific genetic alterations was incriminated in acquired methotrexate resistance of osteosarcomas. In particular increased expression of dihydrofolate reductase was demonstrated in 62% of cases after surgery.

**References**


This article should be referenced as such: