Epidemiology and classification of bone tumors

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Summary

Primary bone tumors are uncommon and this has certainly contributed to the scarcity of data about their relative frequency, and to the limited understanding of the risk factors. Overall, bone sarcomas account for 0.2% of all malignancies, and the adjusted incidence rate for all bone and joint malignancies is 0.9 per 100,000 persons per year, while the 5-year overall survival rate is 67.9%. The age specific incidence rates of bone sarcomas show a bimodal distribution, with a first peak occurring in the second decade, and a second peak occurring in patients older than sixty, in relation with the age distribution of the main histological subtypes. Several bone tumor types occur in the setting of inherited syndromes, while some other develop in association with non-neoplastic precursors or in the setting of previous benign tumors. In recent years, significant advances have occurred in the molecular and cytogenetic characterization of benign and malignant bone tumors. The detection of clonal chromosomal aberrations, specific molecular genetic changes, and the identification of growth related tumor cell signaling pathways have resulted in a better understanding of the pathogenesis of several neoplastic entities, and have provided the basis for an improvement in the diagnostic workup and differential diagnosis of several bone tumors presenting with overlapping clinical, radiological and pathological features, as well as for the identification of new prognostic factors and therapeutic targets.

KEY WORDS: bone tumors; epidemiology; classification; pathology.

Epidemiology of bone tumors

Primary bone tumors are relatively uncommon and this has certainly limited the collection of data about their relative frequency and to the insufficient understanding of the risk factors. Although the incidence of benign bone tumors is higher than the incidence of primary malignant tumors, it is likely that benign lesions are underestimated because they often are asymptomatic and not clinically recognized. In addition, primary bone tumors are outnumbered by metastases from carcinomas, melanoma, or hematologic malignancies, such as plasmacytoma.

According to the analysis of the Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review of the National Cancer Institute, it is estimated that 2,810 men and women (1,620 men and 1,190 women) will be diagnosed with and 1,490 men and women will die of cancer of the bones and joints in 2011 (1). Overall, bone sarcomas account for 0.2% of all malignancies diagnosed in the United States, and the age adjusted incidence rate for all bone and joint malignancies is 0.9 per 100,000 persons per year. The overall 5-year relative survival for 2001-2007 was 66.3% and the age-adjusted death rate based on patients who died in 2004-2008 in the US, was 0.4 per 100,000 men and women per year (1).

In Italy, according to the 2006 report on tumors by the AIRTUM (Association of Italian Tumor Registries) primary malignant bone tumors represented 0.2% of all malignancies diagnosed in males and females in the period 1998-2002, while mortality represented 0.3% of all cancer deaths in both sexes in the same period (2). In the area covered by the Italian Network of Cancer Registries, there were on average 1.3 new bone malignant tumors diagnosed per 100,000 males/year and 1.1 per 100,000 females/year (2). Overall, in the year 2002, there were 208 deaths in Italy due to bone cancer among males and 145 among females. As expected, bone cancer was relevant among young subjects, since more than 50% of cases were diagnosed before the age of 59 years (2). The cumulative risk (0-74 years) of developing a bone cancer was 0.9‰ among males (1 case every 1,099 men) and about 0.7‰ among females (1 case every 1,370 women) while the cumulative risk of dying from this cancer was 0.5‰ among males and 0.4‰ among females, respectively (2). Incidence rates for primary malignant tumors of bone vary considerably across Italy, with a ratio between areas with higher and lower rates of approximately 3 to 4 times (2). These differences may be explained, at least in part, by the use of different coding rules for the bone site, which may have determined the inclusion, especially for cancer deaths, of secondary tumors (2). Considering time trends, bone cancer shows a stable incidence over time, while mortality is decreasing. The most frequently diagnosed histologic subtypes were chondrosarcoma (30% in males and 29% in females), osteosarcoma (16% in males and 17% in females) Ewing's sarcoma (14% in both males and females) and chordoma (8% in males and 5% in females) (2).

The age specific incidence rates of bone sarcomas typically show a bimodal distribution, with a first peak occurring in the second decade, and a second peak occurring in patients older than sixty years of age. This is related to the different age distribution of the main histological subtypes, since Ewing's sarcoma and osteosarcoma are the most frequent

histologic subtypes in the first two decades, while chondrosarcoma, malignant fibrous histiocytoma, chordoma and secondary osteosarcoma show an increased incidence after the fourth decade. On the other hand, the majority of benign bone tumors and tumor-like lesions occur in the first two decades of life. In general, there is no significant gender predilection, although some tumors (e.g. Paget's sarcoma, chordoma) show a higher prevalence in males. According to SEER data, in the period 2004-2008, the median age at diagnosis for cancer of the bones and joints was 40 years of age. Approximately 29.0% were diagnosed under age 20; 15.4% between 20 and 34; 10.5% between 35 and 44; 13.0% between 45 and 54; 11.4% between 55 and 64; 8.3% between 65 and 74; 9.1% between 75 and 84; and 3.5% over 85 years of age (1).

Several bone tumors may occur in the setting of inherited syndromes, but their histopathologic features do not differ from those of sporadic cases (3, 4). Moreover, although the majority of primary bone malignancies arise de novo, there is increasing evidence that some develop in association with non-neoplastic precursors or in the setting of previous benign tumors. Paget's disease of bone, previous radiation therapy, and cartilaginous dysplasias are some of the most well known precancerous conditions for the development of bone sarcomas. The risk of developing a primary malignant tumor of bone is variable according to the related condition (5). High risk precursors are represented by Ollier's disease and Maffucci syndrome, familial retinoblastoma syndrome and Rothmund Thompson syndrome, while conditions representing a moderate risk include multiple osteochondromas, Paget's disease and radiation osteitis. A low risk for malignant transformation has been associated with fibrous dysplasia, bone infarct, chronic osteomyelitis, prosthetic implants, osteogenesis imperfecta, giant cell tumor, osteoblastoma and chondroblastoma (5).

The classification of bone tumors

In general, a widely accepted histopathological classification responds to the need of using reproducible diagnostic criteria and categories, which is a prerequisite for the prediction of the biological potential of a tumor, thus finally representing a guide for treatment. Moreover, a consistent classification of tumors allows to understand their intrinsic biology and to identify specific phenotypes and genetic alterations, which in turn may help in the diagnosis.

Bone tumors are currently classified according to the line of differentiation of neoplastic cells and their resemblance to normal counterparts. These criteria can be easily applied to cartilage-forming or bone-forming tumors, while others lack a recognizable differentiation that can link them to a normal tissue, like for example Ewing's sarcoma. Another key aspect to be considered is that the cell of origin of mesenchymal tumors is unknown. Moreover, no precursor lesions have been identified, unlike epithelial tumors, which often recognize a multistep process of carcinogenesis. It is largely believed that sarcomagenesis occurs through molecular alterations affecting mesenchymal stem cells ultimately inducing a neoplastic differentiation program, which further results in a specific phenotype. On these bases, the current WHO classification of primary bone tumors has abandoned the concepts of histogenesis and cell of origin of the tumor, to focus on a combination of parameters that include morphology, phenotype and genotype (5).

Primary benign and malignant bone tumors are grouped in 15 different categories, including cartilage, osteogenic, fibrogenic, fibrohistiocytic, hematopoietic, giant cell, notochordal, smooth muscle, vascular, lipogenic, and neural tumors, Ewing sarcoma/primitive neuroectodermal tumor, miscellaneous tumors and lesions, and joint lesions. At variance with the classification scheme adopted for soft tissue tumors, only benign and malignant categories are recognized, while in the former a group of tumors with intermediate behavior is included. However, the introduction of a category of tumors with intermediate behavior, both locally aggressive and rarely metastasizing, could improve this scheme, with regards for example to giant cell tumor of bone, which is currently classified as a benign tumor, or to some vascular neoplasms, like epithelioid hemangioma (6).

Evolving concepts and new entities

The advances in the characterization of the molecular phenotype of tumor cells has determined relevant changes in the classification schemes, with the disappearance of some entities and the inclusion of new ones. Moreover, after the publication of the WHO classification of bone and soft tissue tumors, new emerging entities, as well as older ones, have been characterized and reported, and these will be probably included in the next revision of this classification. Hereafter, some examples are discussed.

Hemangiopericytoma of bone is no longer recognized as a true separate entity, but rather as a morphological growth pattern which is common to different tumor types, including infantile myofibromatosis, phosphaturic mesenchymal tumor, synovial sarcoma, solitary fibrous tumor among primary tumors, and metastatic meningioma among secondary ones (7). Another tumor type whose existence as a separate true diagnostic category has been deeply reconsidered in the past decades is malignant fibrous histiocytoma (MFH). Indeed, since fibroblast and its variants are the predominant cell types found in these tumors, it has been suggested that the diagnostic entity MFH should be rather classified as a pleomorphic fibrosarcoma (8). Moreover, the use of ancillary techniques, including immunohistochemistry and electron microscopy, may help to more precisely classify high grade pleomorphic sarcomas in specific categories, such as for example leiomyosarcoma or myofibrosarcoma, or to recognize metastatic tumors, such as melanoma or sarcomatoid carcinoma.

Another recent interesting advance in the field of bone and soft tissue tumors, has been the recognition that myoepithelial neoplasms may occur primarily at these sites, which are otherwise entirely devoid of myoepithelial cells. This further underlines the concept of a non-feasibility of a histogenetic approach to the classification of bone and soft tissue tumors. Indeed, these tumors show the same morphological spectrum as their salivary gland counterparts, including the presence of an epithelial component, in which case they are better regarded as mixed tumors. They occur both in adults and in children, and, in most cases, behave in a benign/locally aggressive fashion (9). A subset of these lesions shows features of malignancy and follows a metastasizing clinical course (10). Recently, it has been shown that primary myoepitheliomas of bone frequently present EWSR1 gene rearrangement, a feature that could be useful in the diagnosis of difficult cases (11).

The WHO classification currently recognizes chordoma, which is defined as a low to intermediate grade malignant tumor that recapitulates notochord, as the only member of the group of tumors of the notochord (5). However, several reports support the existence of notochord-type lesions of the axial skeleton that are radiologically and histologically distinct from chordoma (12, 13). These lesions appear to be

benign and should therefore be recognized by radiologists and pathologists and treated conservatively. The relationship of these lesions to chordoma remains an open question, although it has been suggested that these benign lesions may undergo malignant transformation to classic chordomas (12, 13).

Oncogenic osteomalacia is an unusual variant of osteomalacia, in which systemic bone demineralization is determined by and may be cured by resection of a neoplasm. Although most examples reported in the literature of this rare disease have been associated with soft tissue and bone tumors of various types, it has been recently recognized that many of these tumors have, indeed, a quite distinctive histological appearance (14). They are characterized by an admixture of spindle cells, osteoclast-like giant cells, microcysts, ectatic blood vessels, cartilage-like matrix, and bone formation. The term "phosphaturic mesenchymal tumor, mixed connective tissue variant" (PMTMCT) has been coined to describe these unique lesions. These tumors overexpress fibroblast growth factor-23 (FGF-23), a recently described protein capable of inhibiting renal tubular epithelial phosphate transport, and this is now thought to be the pathogenetic mechanism underlying most cases of oncogenic osteomalacia. Immunohistochemistry and RT-PCR for FGF23 has been recognized as a sensitive and specific method for confirming the diagnosis of PMTMCT both in patients with and without oncogenic osteomalacia (14, 15). Improved recognition of the histologic spectrum of these tumors, including the existence of malignant forms, should allow distinction from other mesenchymal tumors (14). The correct diagnosis of PMTMCT is critical, as complete resection cures intractable oncogenic osteomalacia.

The contribution of genetics to the diagnosis and classification of bone tumors

In recent years, an increasing amount of genetic data has become available for bone tumors, which had a profound impact on their diagnosis and classification. Although the majority of primary malignant bone tumors, including osteosarcoma, chondrosarcoma and chordoma, carry nonspecific genetic changes within a background of a complex karyotype, others, like Ewing's sarcoma, present tumor-specific chromosomal translocation. The identification of tumor specific translocations in Ewing's sarcoma, mainly the t (11;22)(q24;q12), have had a major impact in understanding the pathogenesis of this enigmatic small blue round cell tumor, and furnished the basis for its classification as tumor with neuroectodermal differentiation. Moreover, tumor specific translocations such as those identified in Ewing's sarcoma represent a molecular diagnostic tool to assist the pathologist in the diagnosis and in detecting minimal residual disease.

More recently, further molecular abnormalities have been identified in primary bone tumors, some of which appear characteristic of single tumor types. These findings are fostering new changes in the classification of bone tumors. A significant example may be aneurysmal bone cyst (ABC). This is a benign bone lesion described in 1942 by Jaffe and Lichtenstein and until recently considered as a reactive process with the potential for local recurrence. The term secondary ABC has been used to designate those lesions occurring in association with other processes, mainly fibrous dysplasia, chondroblastoma, osteoblastoma and giant cell tumor of bone. The identification of a recurrent chromosomal translocation t (16;17)(q22; p13) has supported the notion that at least a subset of ABC have a neoplastic nature (16-18). This translocation fuses the promoter region of the osteoblast cadherin 11 gene (CDH11) on chromosome 16q22 to the entire coding sequence of the ubiquitin protease TRE17/USP6 gene on chromosome 17p13 (19). Interestingly, this translocation is present only in the spindle cell component of primary ABC, and it is not detected in secondary ABC. Recent observations indicate that the cells affected by TRE17 rearrangement and overexpression in ABC are indeed immature osteoblasts (20), and that TRE17 appears to simultaneously inhibit osteoblast maturation and stimulate osteoclast activity, thus favoring the growth of ABC. Altogether, these findings support the notion that primary ABC is a mesenchymal neoplasm possibly of the osteoblastic lineage, whereas secondary ABC, although morphologically similar to primary ABC, most likely represents a common endpoint of differentiation in various non-ABC bone tumors.

Conclusions

Primary malignant bone tumors are rare and as such they represent a difficult category of tumors for appropriate recognition, classification and treatment. Although the occurrence of bone sarcomas is low, they affect particularly children and adolescents, which implies that they have a major impact on the life of patients and their families. In recent years, advances in medical and surgical treatment modalities have resulted in an improvement of the outcome and survival of primary malignant bone tumors. This has been paralleled by significant developments in the molecular and cytogenetic characterization, which in combination with light/electron microscopy and immunohistochemical techniques, has contributed to a better understanding of this group of tumors.

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