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EPIDEMIOLOGY OF BONE TUMORS

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Resume

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.

Keywords: bone tumors, epidemiology, classification, pathology

Резюме

Первичные опухоли костей встречаются редко, и это, безусловно, способствовало нехватке данных об их относительной частоте и ограниченному пониманию факторов риска. В целом, на костные саркомы приходится 0,2% всех злокачественных опухолей, а скорректированная заболеваемость всех злокачественных опухолей костей и суставов составляет 0,9 на 100 000 человек в год, в то время как общая 5-летняя выживаемость составляет 67,9%. Возрастные показатели заболеваемости саркомами костей демонстрируют бимодальное распределение, причем первый пик приходится на второе десятилетие, а второй пик встречается у пациентов старше шестидесяти лет в зависимости от возрастного распределения основных гистологических подтипов. Некоторые типы опухолей костей возникают на фоне наследственных синдромов, в то время как другие развиваются в ассоциации с неопластическими предшественниками или на фоне предшествующих доброкачественных опухолей. В последние годы были достигнуты значительные успехи в молекулярной и цитогенетической характеристике доброкачественных и злокачественных опухолей костей. Выявление клональных хромосомных аберраций, специфических молекулярно-генетических изменений и выявление связанных с ростом путей сигнализации опухолевых клеток привело к лучшему пониманию патогенеза ряда новообразований, а также послужило основой для улучшения диагностической работы и дифференциальной диагностики ряда опухолей костей с перекрывающимися клиническими, рентгенологическими и патологическими признаками, а также для выявления новых прогностических факторов и терапевтических мишеней.

Ключевые слова: опухоли костей, эпидемиология, классификация, патология

Резюме

Бирламчи суяк ўсмалари кам учрайди ва бу, албатта, уларнинг нисбий частотаси тўғрисидаги маълумотларнинг камлигига ва хавф омилларининг чекланган тушунчасига ҳисса қўшди. Умуман олганда, суяк саркомалари барча

хавфли ўсмаларнинг 0,2 фоизини ташкил этади ва барча суяк ва бўғим хавфли ўсмалари учун тузатилган касалланиш даражаси йилига 100 000 кишига 0,9 ни ташкил қилади, 5 йиллик умумий омон қолиш даражаси эса 67,9 фоизни ташкил этади. Суяк саркомасининг ёшга боғлиқ частотаси асосий гистологик субтипларнинг ёшга боғлиқ тақсимланиши билан боғлиқ ҳолда бимодал тақсимланишни кўрсатади, биринчи чўққи иккинчи ўн йилликда, иккинчи чўққи эса олтмиш ёшдан ошган беморларда учрайди. Суяк ўсмаларининг бир қанча турлари ирсий синдромлар маҳалида пайдо бўлса, баъзи бир турлари неопластик бўлмаган ўтмишдошлар билан бир ассоциацияда ёки илгари пайдо бўлган хавфсиз ўсмалар маҳалида пайдо бўлади. Сўнгги йилларда суякнинг хавфсиз ва хавфли ўсмаларини молекуляр ва ситогенетик тавсифлашда сезиларли ютуқларга эришилди. Клонал хромосома аберрациялари, ўзига хос молекуляр-генетик ўзгаришларни аниқлаш ва ўсиш билан боғлиқ ўсма ҳужайраларининг сигнализация йўлларини аниқлаш бир қатор неопластик тузилмалар патогенезини яхшироқ тушунишга олиб келди ва бир-бирига ўхшаш клиник, рентгенологик ва патологик хусусиятларга эга бўлган бир нечта суяк ўсмаларини ташхислаш ва дифференциал ташхислашни такомиллаштириш, шунингдек, янги прогностик омиллар ва терапевтик мақсадларни аниқлаш учун асос бўлди.

Калит сўзлар: суяк ўсмалари, эпидемиологияси, таснифи, патологияси

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[7].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 [1,2].

In Italy, according to the 2006 report on tumors by the AIR-TUM (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 [11].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 [3].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 [12].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 [17]. 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 [8].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 [14]. 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) [11].

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 [5,9,10].

Osteosarcoma derives from primitive bone-forming mesenchymal cells and is the most common primary bone malignancy. The incidence rates and 95% confidence intervals of osteosarcoma for all races and both sexes are 4.0 (3.5-4.6) for the range 0-14 years and 5.0 (4.6-5.6) for the range 0-19 years per year per million persons. Among childhood cancers, osteosarcoma occurs eighth in general incidence and in the following order: leukemia (30%), brain and other nervous system cancers (22.3%), neuroblastoma (7.3%), Wilms tumor (5.6%), Non-Hodgkin lymphoma (4.5%), rhabdomyosarcoma (3.1%), retinoblastoma (2.8%), osteosarcoma (2.4%), and Ewing sarcoma (1.4%). [4]. The incidence rates of childhood and adolescent osteosarcoma with 95% confidence intervals areas follows: Blacks, 6.8/year/million; Hispanics, 6.5/year/million; and Caucasians, 4.6/year/million. Osteosarcoma has a bimodal age distribution, having the first peak during adolescence and the second peak in older adulthood. The first peak is in the 10-14-year-old age group, coinciding with the pubertal growth spurt. This suggests a close relationship between the adolescent growth

spurt and osteosarcoma. The second osteosarcoma peak is in adults older than 65 years of age; it is more likely to represent a second malignancy, frequently related to Paget's disease. [13].The incidence of osteosarcoma has always been considered to be higher in males than in females, occurring at a rate of 5.4 per million persons per year in males vs. 4.0 per million in females, with a higher incidence in blacks (6.8 per million persons per year) and Hispanics (6.5 per million), than in whites (4.6 per million). Osteosarcoma commonly occurs in the long bones of the extremities near the metaphyseal growth plates. [18].The most common sites are the femur (42%, with 75% of tumors in the distal femur), the tibia (19%, with 80% of tumors in the proximal tibia), and the humerus (10%, with 90% of tumors in the proximal humerus). Other likely locations are the skull or jaw (8%) and the pelvis (8%). Cancer deaths due to bone and joint malignant neoplasms represent 8.9% of all childhood and adolescent cancer deaths. Death rates for osteosarcoma have been declining by about 1.3% per year. The overall 5-year survival rate for osteosarcoma is 68%, without significant gender difference. The age of the patient is correlated with the survival, with the poorest survival among older patients. Complete surgical excision is important to ensure an optimum outcome. Tumor staging, presence of metastases, local recurrence, chemotherapy regimen, anatomic location, size of the tumor, and percentage of tumor cells destroyed after neoadjuvant chemotherapy have effects on the outcome [16,17].

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 [5,7].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 [16,17].

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. 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. 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, 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 [11,15,17].

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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