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Comparative Analysis of the Effectiveness of Combined Treatment of Osteogenic Sarcoma in Tubular Bones in Children

Iskandarov Kamol Zayniddinovich[1,*], Islomov Sarvar Temurovich[2], Sayitov Begali Shokir Ugli[3], Rustamova Xilola Mirzakarimovna[3]

[1]Head of the Department "Oncology and Hematology", National Children's Medical Center, 294 Parkent street, Tashkent, Uzbekistan
[2]Scientific Researcher, Department "Oncology and Hematology", National Children's Medical Center, 294 Parkent Street, Tashkent, Uzbekistan
[3]Department "Oncology and Hematology", National Children's Medical Center, 294 Parkent street, Tashkent, Uzbekistan

Abstract One of the most prevalent primary malignant bone tumours in children and adolescents is classical osteosarcoma. The metaphysis accounts for 90% of tumour localization in long tubular bones, with the diaphysis accounting for 9% and the epiphysis accounting for a very rare occurrence of tumours. The clinical, radiographic, and histological diagnosis of classical (conventional) osteosarcoma in children and adolescents is covered in this article. Genetic abnormalities, differential diagnosis, and the prognosis for this pathology are also briefly discussed.

Keywords Osteosarcoma, Method, Diagnosis, Treatment, Children and adolescents

1. Introduction

Osteosarcoma is a malignant osteogenic tumor consisting of neoplastic cells that produce osteoid or a substance histologically indistinguishable from it in at least one visual field [1]. According to the WHO classification, there are several options:

1. Central osteosarcoma (low-grade).
2. Classic (conventional) osteosarcoma.
3. Telangiectatic osteosarcoma.
4. Small cell osteosarcoma.
5. Secondary osteosarcoma.
6. Paraosteal osteosarcoma.
7. Periosteal osteosarcoma.
8. Superficial osteosarcoma (high-grade).

2. Materials and Methods

Classic osteosarcoma is an intraosseous malignant tumor whose cells produce bone. It is considered primary if it develops in unchanged bone, and secondary if it develops against the background of radiation, Paget's disease, etc.

Classic osteosarcoma is the most common high-grade primary sarcoma affecting bone [2]. Despite this, it accounts for less than 1% of all malignant tumors occurring in the US population [2,3]. The incidence rate is from 10 to 26 new cases per 1 million population of the planet per year [4]. Has a bimodal age distribution. The first peak is in the age group of 10-14 years, the second - at the age of over 40 years. It is extremely rare in children under 5 years of age [5]. Gender distribution favors the male population with a ratio of 1.35:1. As a result of malignant transformation, Paget's disease occurs in approximately 1% of cases, more often in patients with multiple bone lesions, with a peak in the 7th decade of life and accounts for up to half of all cases of osteosarcoma in patients over 60 years of age. Osteosarcoma is the most common radiation-induced sarcoma (2.7–5.5% of all osteosarcomas), most often in patients over 40 years of age. Less commonly associated with benign tumors and tumor-like bone lesions (fibrous dysplasia, simple bone cyst) and metal prostheses. In the study by L. Mirabello et al [3], primary osteosarcoma was 88%, secondary - 10%, and as a consequence of Paget's disease - 2%. Cases of secondary osteosarcoma in children after complex treatment of acute lymphoblastic leukemia and gamma/delta T-cell lymphoma have been described [2].

3. Results and Discussion

The etiology of osteosarcoma is unknown. It occurs de novo without any predisposing factors. May appear after injury or foreign body (orthopedic implants) [1]. There is evidence of

* Corresponding author:
dr_kamol@mail.ru (Iskandarov Kamol Zayniddinovich)
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an increased risk of osteosarcoma in children with a birth weight of more than 4046 g and height above average [3]. It is believed to develop from a mesenchymal stem cell with minimal osteoblastic differentiation, but the "cell of origin" remains unknown [4]. It is observed more often among various genetically determined syndromes: Li-Fraumeni, congenital retinoblastoma, Rothmund-Thomson, Diamond Blackfan anemia, Bloom, Werner syndrome and others [5].

May occur in various bones. However, more often in the long tubular bones of the extremities [3], especially in the distal part of the femur (30%), proximal part of the tibia (15%), and proximal part of the humerus (15%). These localizations are due to the greatest proliferation of the "growth plate". In long tubular bones, the tumor is usually localized in the metaphysis (90%), less often in the diaphysis (9%) and extremely rarely in the epiphysis. Tumors localized in the jaws, pelvic bones and vertebrae are usually observed in older age groups. When the jaws are affected, the tumor is more common in the lower jaw than in the upper jaw (58 and 42%, respectively) [1]. Involvement of small skeletal bones in the pathological process is rare [2]. Multifocal lesions occur in Paget's disease in 15-20% of cases. However, the question still remains open whether this is a primary multiple or metastatic lesion.

Clinically manifested by a progressive increase in the volume of the affected part of the body. The concern is deep, growing pain, sometimes for several weeks or months. The skin over the tumor may be hyperemic, edematous, with an accentuated venous pattern. In advanced cases, ulceration of the skin over the tumor is observed (Fig. 1).

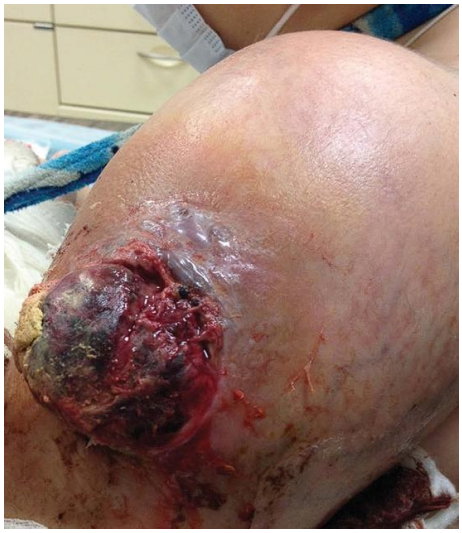

Figure 1. Classic osteosarcoma of the humerus with damage to the soft tissues of the shoulder and an extensive ulcerative skin defect. Boy, 9 years old

Due to the large volume of the lesion, movements in the corresponding joint may be limited, and effusion into the joint cavity. Weight loss and cachexia are sometimes observed. Pathological fractures are recorded in 5-10% of cases. There is evidence that in children under 5 years of age, diaphyseal localization is more common, the disease is more aggressive and responds worse to chemotherapy [3].

The X-ray picture of classical osteosarcoma can vary widely. Typically, a large tumor is detected, destroying the periosteum and the affected bone (lytic component), poorly limited, with a massive soft tissue component (Fig. 2).

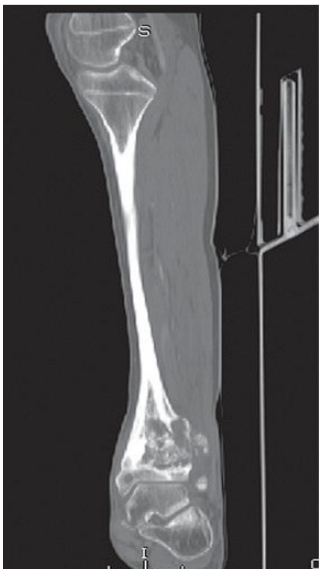

Figure 2. Classic osteosarcoma of the distal epiphysis and metaphysis of the tibia. The destruction of the periosteum is determined, the soft tissue component of the tumor is clearly visible

A so-called cloud-like pattern is often detected due to uneven ossification of the tumor. Most tumors in children that arise in the metaphyseal zone involve the growth plate in the pathological process, which complicates surgical resection and leads to disruption of the synchronous growth of the limb.

On histological examination, classical osteosarcoma has a fairly wide range of morphological changes. The tumor grows along the bone marrow spaces, replacing the latter. Surrounds and destroys normal bone trabeculae. Neoplastic cells are usually characterized by moderate cellular atypia and pleomorphism. The shape can be epithelioid, plasmacytoid, spindle-shaped and/or round. The cytoplasm is often eosinophilic and may be light-colored. A mandatory histological criterion for diagnosing "classical osteosarcoma" is the detection of neoplastic bone tissue (pathological osteoid). Moreover, the amount of pathological osteoid does not matter, since it varies widely in different fields of view. This osteoid is produced by neoplastic cells and is topographically found adjacent to and/or surrounding them. It can form a resemblance to primitive spongy bone with a chaotic spatial orientation of "neoplastic" trabeculae. Non-mineralized deposits of pathological osteoid are stained with eosin, mineralized deposits are basophilic. It is quite difficult to reliably distinguish non-mineralized pathological bone matrix (osteoid) from another extracellular matrix (collagen). With a high microscope magnification (×400), examining collagen, one can detect fibrillarity; the osteoid is more homogeneous.

In accordance with the specific histological features, according to the 2013 WHO classification [2], classical osteosarcoma is divided into several histological variants:

1) osteoblastic (including sclerosing);
2) chondroblastic;
3) fibroblastic;
4) rich in giant cells (giant cell);
5) osteoblastoma-like;
6) epithelioid;
7) clear cell;
8) chondroblastoma-like.

However, despite the identification of these histological variants, no differences in the course and prognosis of the disease were identified. Osteoblastic, chondroblastic and fibroblastic variants are most often found within the same tumor. The histological subtype is determined based on the predominant pattern in the tumor. The osteoblastic variant occurs in 76-80% of cases, chondroblastic - in 10-13%, fibroblastic - in 10%.

In the osteoblastic variant, "neoplastic" bone predominates in the form of pathological osteoid produced by tumor cells. Areas are found that resemble compact bone in structure (sclerosing type).

In the chondroblastic variant, zones with chondrodifferentiation in the form of neoplastic hyaline cartilage (high-grade) predominate. There may be myxoid areas, more often when the jaws are affected. Neoplastic cells with a chondrocyte phenotype, with pronounced cellular atypia, lie in the lacunar spaces of the cartilaginous hyaline matrix or are located singly or in the form of cords in the myxoid matrix. The cartilaginous component may be predominant or found in the form of separate foci.

In the fibroblastic variant, neoplastic cells are usually spindle-shaped and less often have an epithelioid phenotype. In most cases, cellular atypia is expressed. Tumor cells are associated with extracellular collagen, together with which they often form a storiform pattern (previously known as a variant resembling malignant fibrous histiocytoma). Cells with fibrillar eosinophilic cytoplasm, myofibroblastic differentiation. Osteoclast-like multinucleated cells are not true tumor cells and can be detected in different fields of view in different concentrations.

Repeated amplifications and increases in the copy number of certain DNA regions have been identified in several specific regions of chromosomes: 1p36, 1q21-22, 6p12-21, 8q21-24, 12q11-14, 17p11-13, 19q12-13.

Less common are losses of genetic material in regions 3q13, 8p21, 9p13, 13q14 [4].

Frequent deletion or loss of heterozygosity of the 3q13 region is a specific aberration for osteosarcomas (currently also described only in ovarian cancer). The tumor suppressor gene LSAMP (gene limbic system-associated membrane protein), which regulates cell proliferation and presumably plays a leading role in the pathogenesis of tumor development, has been mapped in this region. There is a tendency to associate 3q12 deletion with progression and poor prognosis of the disease [5].

Most of the most widely described and frequently occurring gene amplifications or increases in gene copy number in osteosarcoma are associated with an unfavorable prognosis and disease progression. Amplification and increase in copy number of the 6p12-21 region occurs in 40-50% of cases of this tumor variant. A potential target gene for this region is the RUNX2 gene, which is involved in osteoblast differentiation. High levels of RUNX1 expression are also associated with poor response to therapy [2].

4. Conclusions

The prognosis of osteosarcoma depends on many factors: age, gender, size (volume) of the tumor, location, cleanliness of the surgical resection margin and stage. For example, localized distal involvement of more than 90% of chemotherapy-induced tumor necrosis in combination with radical resection provides a 5-year survival rate of more than 80% of cases. For example, there are studies showing a correlation between the amount of tumor necrosis and prognosis [1], the level of VEGF expression with a worse prognosis and the possibility of using targeted therapy [2]. Some authors report a better prognosis if morphometric examination reveals "large and round" nuclei of neoplastic cells [3]. The prognosis is worse with proximal or axial localization of the tumor, large size, presence of metastases and poor response to preoperative chemotherapy, with tumor localization in the pelvic bones, deviation from the normal body mass index on the body. ment of diagnosis. There are reports on the relationship between the intensity of apoptosis of neoplastic cells and prognosis.

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