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Approach to Primary Vertebral Tumors in the Light of the 2020 Updated World Health Organization Classification of Bone Tumors

Ilkay TOSUN[1], Sait NADERI[2]

[1]Umraniye Education and Research Hospital, Department of Pathology, Istanbul, Turkey
[2]QBmed, Istanbul Brain and Spine Center, Department of Neurosurgery, Istanbul, Turkey

Corresponding author: Ilkay TOSUN ✉ milkaytosun@hotmail.com

ABSTRACT

AIM: To define a new approach for primary vertebral tumors by discussing them in the light of 2020 World Health Organization (WHO) classification of bone tumors.

MATERIAL and METHODS: In this study, we have discussed primary vertebral tumors in light of the 2020 Updated WHO Classification of Soft Tissue and Bone Tumors.

RESULTS: Chondroblastoma and chondromyxoid fibroma has been classified in the benign category, while synovial chondromatosis has been moved from the benign category to the intermediate category. In the updated classification, grade I chondrosarcoma has been classified in the malignant category with grade II–III chondrosarcomas. Minor amendments have been made for osteosarcoma subtypes. Neoplasms of undetermined origin, such as aneurysmal cysts, simple bone cysts, fibrosis dysplasia, and osteofibrous dysplasia, have been classified as neoplastic lesions. Chordomas have been classified into "not otherwise stated," poorly differentiated chordomas, and dedifferentiated chordomas. Ewing's sarcomas have been classified in a separate section for undifferentiated, small, round cell sarcomas of the bone and soft tissue. In this section, three distinct subsets different from Ewing's sarcoma have been discussed. CIC-rearranged sarcoma, BCOR-rearranged sarcoma, and round cell sarcomas with EWSR1 gene fusion with non-ETS family members.

CONCLUSION: In this study, we have reviewed the new classifications and discussed their effect on decision making in spinal oncologic surgery.

KEYWORDS: Bone tumor, Classification, Spinal tumor, World Health Organization 2020

ABBREVIATIONS: ETS: E26 transformation specific, **EWSR:** Ewing Sarcoma break point region 1, **FISH:** Fluorescence in situ hybridization, **INI1:** Integrase interactor 1, **NOF:** Non-ossifying fibroma, **NOS:** Not otherwise specified, **RT:** Radiation therapy, **SATB2:** Special AT-rich sequence binding protein 2, **SMARCB1:** SWI/SNF Related Matrix Associated Actin Dependent Regulator of Chromatin, Subfamily B, Member 1, **WHO:** World Health Organization

INTRODUCTION

Oncological surgery of the spine is a major type of spinal surgery. The histopathological features of the tumor play a key role in the decision-making process, selection of surgery type, and postoperative management. In recent years, novel immunohistochemical and molecular biomarkers, that are helpful in identifying the prognosis and selecting the surgical approach, have been described.

As updates in all disciplines, the World Health Organization (WHO) Classification of Soft Tissue and Bone Tumors has been

Ilkay TOSUN : 0000-0001-6655-1014 Sait NADERI : 0000-0002-6784-4270

revised and updated in May 2020. It is of utmost importance to follow such revisions and updates as they may directly affect the treatment of choice at present.

Primary tumors of the spine usually affect children and young adults and are mostly benign in nature. In adulthood, metastatic lesions, rather than primary bone tumors, are generally encountered. The most common benign vertebral tumors include osteoid osteomas, osteoblastomas, giant-cell bone tumors, aneurysmal bone cysts, and hemangiomas, while the most prevalent malignant tumors include osteosarcomas, Ewing's sarcomas, chordomas, and hematolymphoid tumors. For the evaluation of bone tumors located in the vertebral column, the updated WHO classification should be followed. The updated version of the classification (the *5th edition of the WHO Classification of Tumors: Soft Tissue and Bone Tumors*) (5) consists of malignant, intermediate, and benign tumors (Table I).

CHONDROID TUMORS

Chondroblastoma and chondromyxoid fibroma have been moved from the intermediate category to the benign category in the new classification. Synovial chondromatosis has been moved from the benign category to the intermediate category. Grade I chondrosarcoma has been classified into the malignant category with grade II–III chondrosarcomas.

Chondroblastoma

Chondroblastoma is a rare bone tumor that affects the epiphysis of long bones. It accounts for 5% of benign bone tumors and 1.4% of all bone tumors (24). In the *4th edition of the WHO Classification of Tumors: Soft Tissue and Bone Tumors*, chondroblastoma was in the intermediate group with a very low rate of metastasis; however, in the updated version, it has been moved to the benign category. Chondroblastoma is usually seen in patients with skeletal immaturity (age: 10–25 years) and in bones with endochondral ossification (16). It affects male sex more than female sex. It mostly involves the thoracic and lumbar segments and is rarely localized in the vertebra (14). On gross examination, it is usually <5 cm in diameter with sharp margins (24). Microscopically, it has mononuclear cells with eosinophilic matrix (pink cytoplasm) and giant cells consisting of <10 nuclei with a "chicken-wire" appearance, particularly surrounding the mononuclear cells. Immunohistochemical analysis has revealed *H3F3B* positivity. In recent years, *H3F3B* driver mutations have been diagnosed in 90% cases (5).

Chondromyxoid Fibroma

Chondromyxoid fibroma can affect all age groups and localizations; however, long bones (particularly the proximal tibia and distal femur) are the most commonly affected sites. Although extremely rare, it can localize to the vertebra. The main initial findings include persistent pain and swelling around the affected bone (24). In the 2020 update, it has been moved from the locally aggressive intermediate category to the benign category with excellent prognosis, even in recurrent tumors. Radiologically, it shows non-specific features; however, it is benign in nature. Microscopically, it has hypocellular centers and a hypercellular periphery with a micro- and macro-lobular growth pattern showing myxoid variability in the basophilic matrix. These lobules have stellate cells or round, bipolar, or polygonal shaped cells with scattered multinucleated osteoclast-like giant cells. In rare cases, it shows S100 and SOX9 positivity on immunohistochemical staining; however, none of them are diagnostic or disease specific. Molecular diagnostic studies have not been revised in the 2020 update, and translocation on chromosome 6 has been identified in some cases (2).

Synovial Chondromatosis and Chondromatosis

In the previous classification, synovial chondromatosis was in the benign category; however, it has been moved to the locally aggressive intermediate tumor category with chondromatosis in the 2020 update. It usually affects large joints such as the knee joint and is characterized by multiple discrete nodules of varying sizes, presenting as intra-articular loose bodies in gray-white color on the surface lining of the synovial membrane. Although rare, it can localize to the vertebral joints. After ongoing debates for a long time on the metaplastic versus neoplastic nature of chondromatosis, it has been classified as a neoplastic lesion according to the updated WHO classification based on recent molecular diagnostic studies. On microscopic examination, the presence of hypercellular hyaline cartilaginous nodules embedded in the synovial tissue is the hallmark. In molecular studies, *FN1-ACVR2A* and *ACVR2A-FN1* fusions have been detected by fluorescence in situ hybridization (FISH) in up to 50% of cases with benign synovial chondromatosis, but extremely rarely in malignant cases (1). Recurrence is observed in 15%–20% cases. The rate of malignant transformation is very low and is more common in large tumors with frequent recurrences.

Chondrosarcoma

Chondrosarcoma is a malignant mesenchymal tumor with cartilaginous differentiation. Among all primary malignant bone tumors, it ranks second after osteosarcoma. It can be a primary/*de novo* tumor or secondary to a benign cartilaginous lesion in rare cases (22). Enchondroma and chondroblastoma are risk factors for the development of chondrosarcoma. It usually affects adults; however, in cases of secondary chondrosarcomas such as Ollier disease or Maffucci syndrome, it can be observed at younger ages. The main affected sites are the pelvis, femur, humerus, and ribs. Although rare, it can be located in the vertebral canal. The incidence of spinal chondrosarcoma varies from 2% to 12% (12). Radiological findings indicate various appearances depending on the grade of the tumor. In general, the presence of an intramedullary mass, cortical irregularity and thickening, destruction, and soft tissue component is a hallmark of malignancy, and the increased tumor grade obscures the intralesional calcification (24). Chondrosarcomas are classified into three main grades. In the previous classification, grade I chondrosarcomas were classified as locally aggressive intermediate entities; however, in the 2020 WHO classification, they have been moved to the malignant category with grade II–III chondrosarcomas. Chondrosarcomas are divided into three grades according to their

Table I: Fifth Edition of WHO Classification of Tumours: Soft Tissue and Bone Tumours

Chondrogenic Tumours	
Benign	Subungual exostosis Bizarre parosteal osteochondromatous proliferation Periosteal chondroma Enchondroma Osteochondroma Chondroblastoma, NOS Chondromyxoid fibroma Chondroid chordoma Osteochondromyxoma
Intermediate (locally aggressive)	Chondromatosis, NOS Atypical cartilaginous tumour
Malignant	Chondromatosis, Grade I,II,III Periosteal chondrosarcoma Clear cell chondrosarcoma Mesenchymal chondrosarcoma Dedifferentiated chondrosarcoma
Osteogenic Tumours	
Benign	Osteoma, NOS Osteoid osteoma, NOS
Intermediate (locally aggressive)	Osteoblastoma, NOS
Malignant	Low-grade central osteosarcoma Osteosarcoma, NOS (conventional osteosarcoma, telangiectatic osteosarcoma small cell osteosarcoma) Parosteal osteosarcoma Periosteal osteosarcoma High-grade surface osteosarcoma Secondary osteosarcoma
Fibrogenic Tumours	
Intermediate (locally aggressive)	Desmoplastic fibroma
Malignant	Fibrosarcoma, NOS
Vascular Tumours of Bone	
Benign	Hemangioma, NOS Epithelioid hemangioma
Intermediate (locally aggressive)	Epithelioid hemangioendothelioma, NOS
Malignant	Angiosarcoma
Osteoclastic Giant Cell-Rich Tumours	
Benign	Aneurysmal bone cyst Non-ossifying fibromas
Intermediate (locally aggressive, rarely metastatic)	Giant cell tumour of bone, NOS
Malignant	Malignant giant cell tumour of bone
Notochordal Tumours	
Benign	Benign notochordal tumour
Malignant	Chordoma, NOS Poorly differentiated chordoma Dedifferentiated chordoma
Undifferentiated Small Round Cell Sarcomas of Bone	
Ewing's sarcoma Round cell sarcoma with *EWSR1*-non-ETS fusions CIC-rearranged sarcoma BCOR-rearranged sarcoma	
Other Mesenchymal Tumours of Bone	
Benign	Chondromesenchymal hamartoma of chest wall Simple bone cyst Fibrous dysplasia Osteofibrous dysplasia Lipoma, NOS Hibernoma
Intermediate (locally aggressive)	Osteofibrous dysplasia-like adamantinoma Mesenchymoma, NOS
Malignant	Adamantinoma of long bones Dedifferentiated adamantinoma Leiomyosarcoma, NOS Undifferentiated pleomorphic sarcoma
Hematopoietic Tumours of Bone	
Plasmacytoma Non-Hodgkin B and T-cell lymphomas, Hodgkin lymphoma Histiocytosis (Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease	

cellularity, cellular atypia, and mitotic activity. Grade I tumors have similar morphological features to those of enchondromas, and therefore, non-specified enchondromas or grade I chondrosarcomas that could not be differentiated have been classified as atypical cartilaginous tumors/grade I chondrosarcomas. Despite overlapping morphological features, clinical prognosis and surgical treatment are different, and the 2020 WHO update has recommended grade I definition for flat bone tumors (*i.e.*, the pelvis, scapula, and skull base) and atypical cartilaginous tumors for long and short tubular bone tumors (24). Histopathologically, there is typical permeation into the cortical bone and marrow space with entrapment of trabeculae of the mature bones of the host. The diagnosis of grade II–III chondrosarcomas is relatively easy with increased cellularity, cellular atypia, and visible invasion of the surrounding tissue. In addition, the WHO classifies chondrosarcomas into subtypes including periosteal, clear cell, mesenchymal, and dedifferentiated. The treatment for grade I chondrosarcomas is surgery, as for all benign cartilaginous tumors. Wide resection is performed in grade II–III chondrosarcomas. Chemotherapy and radiation therapy (RT) are ineffective in conventional chondrosarcomas, although these treatment modalities are added to the surgical treatment of mesenchymal and dedifferentiated subtypes. Recurrence occurs frequently during the course of the disease (24).

OSTEOGENIC TUMORS

Osteogenic tumors are one of the most common tumors of the spine. No revision has been made in the classification of benign (osteoid osteoma and osteoma) and intermediate (osteoblastoma) tumors in the 2020 WHO update, while minor revisions have been made for malignant (osteosarcoma) tumors.

Osteosarcoma

Osteosarcoma is a malignant mesenchymal tumor characterized by the production of an immature osteoid matrix. It is the most common primary sarcoma of the bone. In the previous classification, osteosarcomas were classified into three subtypes—chondroblastic, fibroblastic, and osteoblastic. However, in the 2020 WHO update, osteosarcomas have been classified into three histological subtypes—conventional, telangiectatic, and small cell under the heading of "not otherwise stated" (NOS). These tumors mostly affect individuals in the second decade of life and are located in the metaphysis of the long bones, particularly in the knee region, and in the spine in 5% cases (7). They can be primary or secondary to the malignant transformation of an existing osteoblastoma or RT (21). Radiological findings include various heterogeneous masses with distinct matrix contents, poorly differentiated margins, and destructive soft tissue invasion. The histopathological features of these tumors vary widely, and the presence of malignant cells producing an osteoid matrix is the hallmark (Figure 1). According to the matrix content, conventional osteosarcomas show chondroid, osteoblastic, or fibroblastic features. The other subtypes are low-grade central osteosarcomas, parosteal and periosteal osteosarcomas, high-grade surface osteosarcomas, and secondary osteosarcomas. The primary treatment for localized osteosarcomas is surgery and chemotherapy. The latter is usually administered as neoadjuvant therapy with the aim of shrinking the tumor size, allowing limb-preserving preventive surgeries with favorable functional outcomes (7).

FIBROGENIC and VASCULAR TUMORS

No revision has been made in the 2020 WHO update.

OSTEOGENIC GIANT CELL-RICH TUMORS

The previous classification included only giant-cell tumors (malignant and benign) in this group. However, aneurysmal bone cysts of undefined neoplastic nature and non-ossifying fibromas (NOFs) have been included in the benign tumor group in the 2020 WHO update.

Aneurysmal Bone Cyst

Aneurysmal bone cysts can be traditionally classified as primary or secondary. Primary cysts refer to neoplastic lesions that are not secondary to other bone tumors, while secondary cysts refer to reactive lesions that develop secondary to another bone tumor. Primary aneurysmal cysts were not classified as neoplastic lesions in the previous WHO classification; however, these cysts have been classified as benign neoplasms in the updated version. They are mostly observed in individuals aged 5–20 years (80%) and are located in the proximal and distal femur, proximal tibia, proximal humerus, and posterior vertebrae in individuals with skeletal immaturity (9). The most frequent symptoms include pain and swelling, and neurological symptoms may appear due to spinal nerve compression in patients with vertebral lesions (5). Radiological appearance is a well-marginated lytic lesion, and the typical fluid–fluid level on magnetic resonance imaging is diagnostic. Histopathological features include fibrous septa with well-defined margins and a blood-filled space without an endothelial lining. The fibrous wall contains giant osteoclastic cells and spindle-shaped cells (Figure 2). Immunohistochemical analysis shows fibrous spaces without

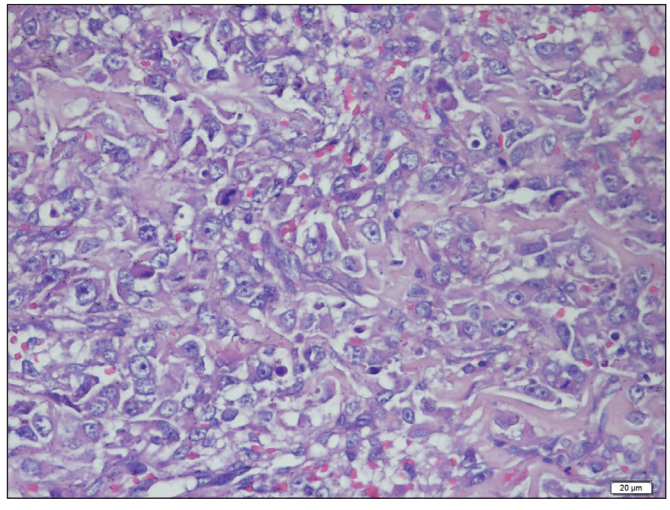

Figure 1: New bone formation between the atypical, mitotically active tumor cells (osteosarcoma) (H&E, x10).

an endothelial lining. The neoplastic nature of these cysts is uncertain. However, recent studies have demonstrated a balanced 17p13 translocation of the *ubiquitin-specific protease* gene in 75% cases (4). This is a critical finding for the differential diagnosis of secondary aneurysmal bone cysts. The local recurrence rate of aneurysmal bone cysts varies between 20% and 70% (5). A solid variant of an aneurysmal bone cyst is characterized by a more solid growth pattern and a higher recurrence rate than classical variant of aneurysmal bone cysts. Giant-cell tumors may complicate the differential diagnosis of these tumors (Figure 3).

NOF

NOFs are benign fibrohistiocytic lesions involving the metaphysis of long bones. It is an eccentric lesion with a sclerotic rim. It typically originates from the metaphysis of long bones and grows toward the diaphysis. Metaphyseal fibrous defects are usually limited to the cortex, while larger lesions extending toward the medulla are defined as NOFs. They are mostly asymptomatic and incidentally diagnosed. Radiological findings include a longitudinal growth pattern and lobulated appearance with sclerotic margins and an intact cortex (10). These tumors are most commonly observed in children and adolescents. Histologically, they show storiform fibrous tissue with uniform spindle fibroblasts, osteoclastic giant cells, and foamy histiocytes. No immunohistochemical or molecular biomarkers have been described thus far. The differential diagnosis includes fibrosis histiocytoma, which has histomorphological features similar to those of NOF. However, it is most commonly observed in individuals in their third decade of life and is located in the extra-metaphyseal bone, which are the discriminative hallmarks of NOF.

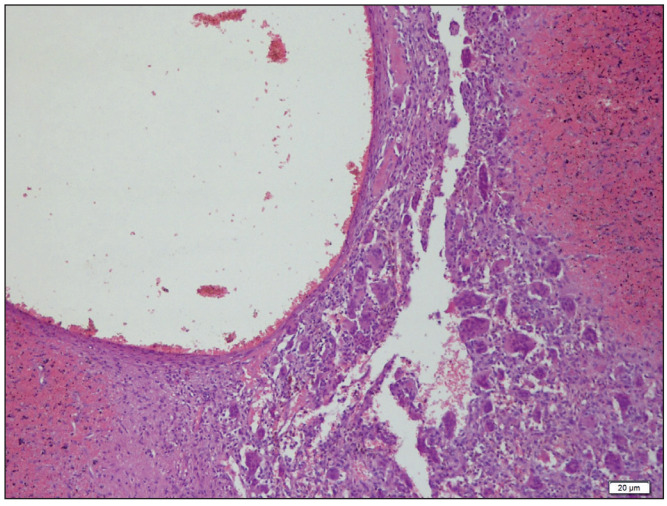

Figure 2: A cystic lesion with a blood-filled space and fibrous wall containing giant cells without endothelial lining (aneurysmal bone cyst) (H&E, x4).

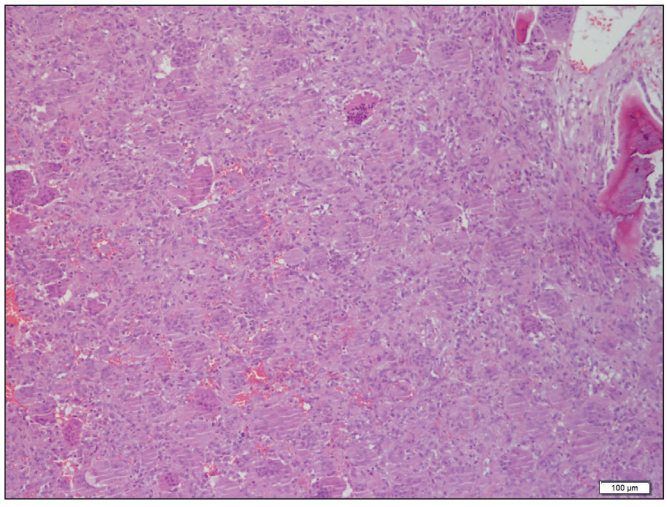

Figure 3: A lesion with multinucleated giant cells and monotonous spindle cells between the bone lamellae (giant cell tumor of the bone) (H&E, x4).

NOTOCHORDAL TUMORS

The notochord forms in the mesoderm after week 3 of embryonic development to regulate the development of the neural plate and vertebral column. It regresses over time during embryonic development and forms the nucleus pulposus (24). Although extremely rare, notochordal remnants can be described in the axial skeleton of children and adults. The presence of these remnants leads to the development of notochord-derived tumors, known as notochordal tumors. In the 2013 WHO classification, notochordal tumors were classified as benign notochordal tumors and malignant chordomas. However, in the 2020 version of the WHO classification, these tumors have been classified into three categories—chordoma (NOS), poorly differentiated chordoma, and dedifferentiated chordoma. This revision highlights the importance that all chordomas should be considered bone sarcomas and require an extralesional approach. The utilization of novel biomarkers, such as *integrase interactor 1* (*INI1*), is recommended to provide information on prognosis.

Chordoma, NOS (conventional chordoma)

It is a rare primary malignant bone tumor that can involve the entire axial skeleton, from the sacrum to the skull base and coccyx. Its incidence is 32% in the skull base, 32.8% in the mobile spine, and 29.2% in the sacrum/coccyx (5). It typically presents with pain and neurological symptoms, and imaging studies reveal lytic and destructive lesions. Histopathological features include epithelioid lesions with abundant clear to eosinophilic cytoplasm that may have a bubbly/multi-vacuolated appearance, forming short cords and nests embedded in the extracellular myxoid matrix (Figure 4). These multi-vacuolated cells are termed physaliphorous cells and appear to be pathognomonic of chordoma. Chondroid chordoma refers to chordoma, in which a large area of the matrix mimics hyaline cartilaginous tumors. Immunohistochemical analysis shows pancytokeratin, S100, vimentin, and EMA staining. In recent years, nuclear staining for Brachyury (Figure 5) has been considered a sensitive and specific biomarker for chondroid chordomas (19). To the best of our knowledge, no molecular testing is available thus far. Tumor size and localization at the time of diagnosis, metastatic status, and

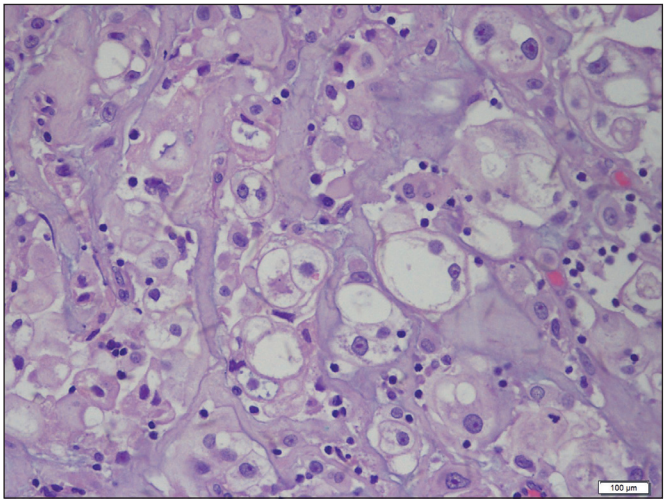

Figure 4: Physaliphorous cells in a nodular lesion embedded in the myxoid stroma with a clear eosinophilic cytoplasm and multivacuolated appearance (chordoma) (H&E, x10).

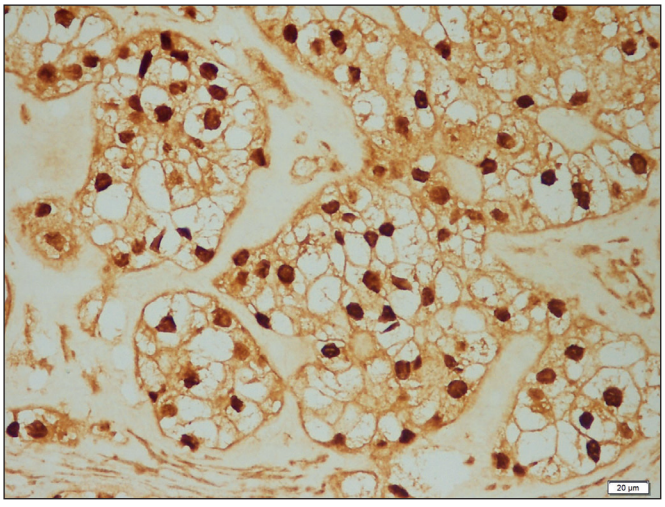

Figure 5: Positive nuclear staining for Brachyury in chordoma (Brachury immunstain, x10).

the presence of distant metastases are determinant factors for the treatment protocol and prognosis. The primary treatment modalities include surgical excision, RT, chemotherapy, and, recently, proton and carbon ion therapy (27). Several studies have investigated the prognostic factors of chordomas. In a histopathological study including 52 patients with chordomas, Yoon et al. (6) found that advanced age and the presence of residual tumor were the most significant prognostic factors. In addition, the chondroid matrix was identified as an independent risk factor for shorter disease-free survival. Although previous studies have demonstrated that sacral chordomas are associated with a poor prognosis, sacral/spinal chordomas have been found to be correlated with a higher survival rate than skull base tumors (6).

Dedifferentiated Chordoma

Dedifferentiated chordoma may arise *de novo* or secondary to conventional chordoma. It shows a biphasic histological pattern, that is, conventional chordoma and high-grade sarcoma. This type of chordoma may present with osteosarcomatous or rhabdomyosarcomatous differentiation. Although the margins are sharp, both tumor types can be intertwined. Nuclear staining for Brachyury is usually negative for dedifferentiated chordomas. Compared to conventional chordoma, its prognosis is poor, with a high mortality rate. In the literature, 87 cases of dedifferentiated chordoma have been reported until 2020, with a median survival of 20 months (11).

Poorly Differentiated Chordoma

Poorly differentiated chordomas are a newly described variant of chordomas that are characterized by a consistent loss of *SWI/SNF Related Matrix Associated Actin Dependent Regulator of Chromatin, Subfamily B, Member 1* (*SMARCB1*) *(INI1)* expression. Until 2019, a total of 53 cases have been described in the literature and have been mostly reported in children and young adults (27). Morphological features show non-typical features of chordoma and physaliphorous cells, but occasional rhabdoid morphology and poor differentiation. Immunohistochemical analysis reveals positive Brachyury staining, and *INI1* expression loss has a high diagnostic value. At the molecular level, it may show INI1 deletion, as assessed by FISH (5). The prognosis is poorer than that of conventional chordomas.

OTHER MESENCHYMAL TUMORS OF THE BONE

In the 2020 WHO update, tumors of undefined neoplastic nature, including simple bone cysts, fibrous dysplasia, and osteofibrous dysplasia, have been classified as neoplastic lesions.

Simple Bone Cyst

A simple bone cyst is a unicameral cystic bone lesion. It is thought to result from blockage in the venous drainage involving the epiphysis injury during skeletal growth and becomes latent after skeletal maturity after it reaches the largest size (26). It is the most common bone lesion in children, and it most frequently affects individuals in their first two decades of life. It usually involves the metaphysis or diaphysis of long bones and is rarely located in the vertebrae (8). Radiographic features include well-defined radiolucent lesions with sclerotic margins. Microscopic examination shows a fibrous cyst wall lacking an epithelial lining with collagen bundles. In addition, fibrin in the wall and outer layer of the wall is compact, forming a cementum-like appearance. Currently, there are no validated immunohistochemical or molecular biomarkers for diagnosis. Most of these cysts spontaneously resolve (20). Curettage with bone grafting is the treatment of choice for symptomatic and large cysts (11).

Fibrous Dysplasia

Fibrous dysplasia is a benign and fibro-osseous bone tumor localized in the medullary bone, characterized by immature bone trabeculae. It may be monostotic (single bone; 70%) or polyostotic (multiple bones) (25). It may affect both children and adults. Craniofacial bones and the femur are the most commonly affected bones and, although rare, vertebral

involvement has been described (17). Radiographic features include typical intramedullary lesions with a ground-glass appearance. Microscopic examination shows bony trabeculae that were abnormally thin and irregular and wavy spicules of woven bone, often displaying a "Chinese character." These spicules are not surrounded by a uniform rim of osteoblasts, which is a critical sign in the distinction from osteofibrous dysplasia in the differential diagnosis. Currently, there are no valid diagnostic immunohistochemical biomarkers. Post-zygotic mutations have been described in the *guanin nucleotide binding protein, alpha stimulating* gene in 93% cases (24).

Osteofibrous Dysplasia

Osteofibrous dysplasia is characterized by trabecular bone woven with fibrous stroma and typical osteoblastic rimming. It usually involves the anterior cortex of the tibia and fibula. It is closely related to fibrous dysplasia; however, osteoblastic rimming is absent in fibrous dysplasia.

Osteofibrous Dysplasia-Like Adamantinoma

Osteofibrous dysplasia-like adamantinoma is classified into the intermediate locally aggressive category. It shows histopathological features similar to those of osteofibrous dysplasia; however, the presence of nests of epithelial cells is a differentiating feature. Epithelial indicators of the adamantinoma component should be used.

HEMATOPOIETIC TUMORS

This group of tumors consists of plasmacytomas, malignant lymphoma, Langerhans cell histiocytosis, Erdheim–Chester disease, and Rosai–Dorfman disease.

UNDIFFERENTIATED SMALL ROUND CELL SARCOMAS OF THE BONE

In the 2013 WHO classification, Ewing's sarcoma was classified in the "Other Tumors" category. Small round cell sarcomas that were previously described as Ewing-like sarcoma/atypical Ewing's sarcoma, but later displayed *Ewing Sarcoma break point region 1* (*EWSR1*) gene fusion with non-E26 transformation specific (ETS) family members based on molecular studies, CIC-rearranged sarcomas, and BCOR-rearranged sarcomas have been classified in this category.

Ewing's Sarcoma

Ewing's sarcoma is the second leading malignant bone tumor in children and young adults. Most cases are present before 20 years of age. The most common sites of involvement are the diaphysis/metaphysis of long bones, pelvis, and ribs (15). Vertebral column involvement is relatively common. In a study including 1,277 patients with Ewing's sarcomas, İlaslan et al. (13) found vertebral column involvement, including involvement of the cervical (3.2%), thoracic (10.5%), lumbar (25%), and sacral regions (53.2%), in 9.8% patients. Regarding its clinical presentation, severe pain and a palpable mass are usually observed, mimicking osteomyelitis. Radiographic features include "moth-eaten" lytic lesions with irregular margins in long bones with soft tissue components, but without osteoid matrix and typical "onion skin" periostitis (15). Microscopic appearance shows nuclei that are uniform, tiny, round, finely dispersed chromatin and scant cytoplasm with positive PAS staining (Figure 6). Immunohistochemical staining reveals strong, diffuse, and membranous CD99 staining (Figure 7), which has a diagnostic value, along with *NKX2-2* and *FLI-1* expression. In particular, diffuse, membranous CD99 staining and *NKX2-2* expression are valuable for definitive diagnosis (3,18). Nonetheless, in cases of atypical localization, a definitive diagnosis can be confirmed by genetic testing. Approximately 85%–90% cases contain a t(11;22) (q24;q12) translocation that fuses the *EWSR1–FLI-1* gene. Approximately 5%–10% cases contain a t(21;22) (q22;q12) translocation, and <1% cases contain a t(7;22)(p22;q12), t(17;22)(q21;q12), or t(2;22)(q35;q12) translocation that fuses the *EWSR1* gene with ETS family members. These translocations form the *EWSR1–ERG, EWSR1–ETV1, EWSR1–ETV4*, or *EWSR1–FEV* fusion genes (15).

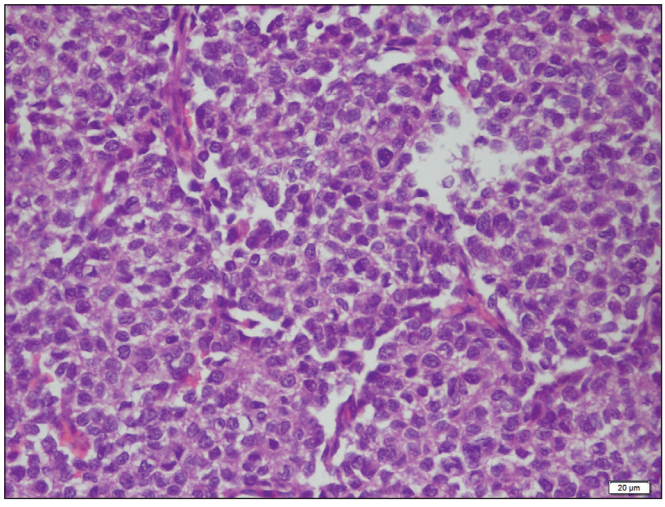

Figure 6: A tumoral lesion showing a diffuse growth pattern with monomorphic, tiny cells (Ewing's sarcoma) (H&E, x4).

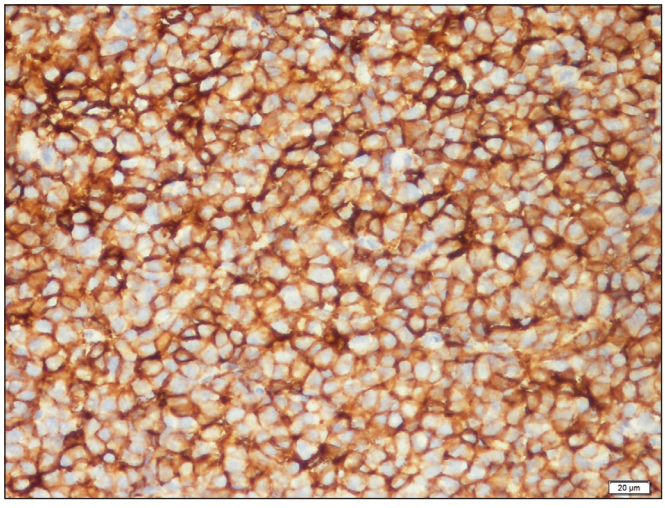

Figure 7: Positive membranous CD99 staining in Ewing's sarcoma (CD99 immunstain, x4).

Round Cell Sarcoma with *EWSR1*–non-ETS Fusions

This sarcoma is rarely characterized by non-ETS family partners containing *EWSR1* (or *FUS*) gene rearrangement. *NFATc2* and *PATZ1* are family partners of *EWSR1/FUS* (5,23). It typically presents as painful and locally aggressive lesions in long bones. It mostly affects children and young adults. Its morphological features are similar, to a certain extent, to those of Ewing's sarcoma with cords and nests, rather than being diffuse in a fibrohyalinized or myxohyalinized background. Nearly half of the cases display membranous CD99 expression in immunohistochemical analysis. The expression of PAX-7 and NKX2-2 has also been identified. At the molecular level, identification of *EWSR–NFTAC2*, *FUS–NFATC2*, and *EWSR1––PATZ-1* fusions is diagnostic. Due to the limited number of cases, data regarding its treatment and prognosis are scarce.

CIC-Rearranged Sarcoma

It is a high-grade, round cell sarcoma with rare primary bone involvement. It affects a wide range of ages, with a male predominance (5). Compared to Ewing's sarcoma, it shows round tumor cells with prominent nucleoli, eosinophilic cytoplasm, and mild pleomorphism, but without neural differentiation. Immunohistochemical analysis shows focal CD99 staining in most cases, while diffuse and membranous CD99 expression can be noted in up to 20% cases. In addition, tumor cells show nuclear ETV4 expression. In genetic testing, the *CIC–DUX4* fusion usually harbors t(4;19) (q35;q13) or (10;19)(q26;q13). In a low number of cases, the *CIC–DUX4* fusion contains a t(X;19) (q13;q13;3) translocation (17). The 5-year survival rate ranges from 17% to 43%, with an aggressive prognosis (5).

BCOR-Rearranged Sarcoma

It is a recently recognized type of sarcoma characterized by rearrangement of the *BCOR* gene. It is more commonly located in the bones than in soft tissues. The most common sites of involvement are the pelvis and lower limbs, and approximately 90% cases present before 20 years of age. Histopathological features are a more prominent round and spindle cell combination than that in Ewing's sarcoma and CIC-rearranged sarcoma. The round cell component typically forms nests, while the spindle cell component is arranged in longer fascicles with a storiform and "herringbone" pattern (17). Immunohistochemical analysis shows strong nuclear BCOR and special AT-rich sequence binding protein 2 (SATB2) staining, but none of them are specific for the diagnosis. In eligible cases, the *BCOR* gene rearrangement and BCOR-ITD should be confirmed via molecular testing, such as reverse transcriptase polymerase chain reaction or FISH in the absence of membranous CD99 staining and in the presence of nuclear BCOR and SATB2 positivity. The 5-year survival rate is comparable with that of Ewing's sarcoma.

CONCLUSION

In summary, advancements in medicine may result in changes in workups and algorithms. WHO classifications have been drawn from clinical results, published case series, and results of new technologies. The new WHO bone classification has increased the understanding of bone tumors, their behavior, and survival. Therefore, it may change our decision-making and surgical strategies. The benign or malignant nature of the tumor affects surgical resection. In most benign lesions, curettage or intralesional resection may be acceptable, whereas malignant spinal tumors require wide extralesional resection.

In the updated classification, chondroblastoma and chondromyxoid fibroma have been classified in the benign category, while synovial chondromatosis has been moved from the benign category to the intermediate category. Grade I chondrosarcoma has been classified in the malignant category with grade II–III chondrosarcomas.

Neoplasms of undetermined origin, such as aneurysmal cysts, simple bone cysts, fibrosis dysplasia, and osteofibrous dysplasia, have been classified as neoplastic lesions in the new classification.

Chordomas are classified into NOS, poorly differentiated chordomas, and dedifferentiated chordomas. Dedifferentiated chordomas show a biphasic histological pattern, that is, conventional chordoma and high-grade sarcoma. This may be problematic for percutaneous biopsy because biopsy from one pattern and skipping other patterns may lead to incorrect diagnosis. Surgeons should be careful and samples from different areas of the tumor should be collected. For the diagnosis of poorly differentiated chordoma, loss of *SMARCB1* (*INI1*) expression is essential. Importantly, chordomas should be evaluated as sarcomas, and wide surgical excision is needed.

AUTHORSHIP CONTRIBUTION

Study conception and design: IT, SN
Data collection: IT, SN
Analysis and interpretation of results: IT
Draft manuscript preparation: IT
Critical revision of the article: IT, SN
Other (study supervision, fundings, materials, etc...): IT
All authors (IT, SN) reviewed the results and approved the final version of the manuscript.

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