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Case Report

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Intensity Modulated Radiotherapy in Giant Cell Bone Tumor and Aneurysmal Bone Cyst-Imaging and Pathohistological Differential Diagnosis and Achieved Long-Term Healing Results after Radiation Therapy

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Abstract

We present two clinical cases in young patients with the rare pathohistological diagnosis of giant cell bone tumor (GCT) and aneurysmal bone cyst (ABC). Against this background, we discuss the rare indications for intensity modulated radiotherapy (IMRT). We focus on the imaging and pathohistological differences, as well as in terms of biological development in these two osteoclastic tumors with a high risk of recurrence after the inability to perform radical operations due to their localization.

Keywords: Giant cell bone tumor, Aneurysmal bone cyst, Intensity modulated radiation therapy, Differential Pathohistological diagnosis

Introduction

Aneurysmal bone cysts (ABC) and giant cell tumors (GCT) are rare and often they are misdiagnosed [1]. Aneurysmal bone cysts (ABC) are aggressive benign lesions, the name of which was first placed by Dr. Jaffe and Lichenstein in 1942 [2,3]. It is an expansive, lytic pseudotumoral bone lesion composed of blood-filled spaces separated by connective tissue septa formed by reactive bone tissue, fibroblasts, and osteoclast-type giant cells [4]. Giant cell bone tumors (GCTs) are rare benign borderline tumors, diagnosed mainly in 30 years old young women [5]. Giant cell tumor (GCT) of bone is a benign locally aggressive tumor whose biological behavior is unpredictable [6]. Pathohistological analysis establishes round or spindle-shaped mononuclear cells mixed with multinucleated giant cells resembling osteoclasts [7,8].The similar image characteristic of these two osteoclastic tumors requires a strict pathohistological diagnosis, determining the complex therapeutic approach. Against the background of two clinical cases, we discuss the differential diagnosis and the assessment of the need for intensity modulated radiotherapy in these rarely diagnosed bone diseases.

Clinical case № 1

We present a 26-year-old patient with a giant sacral tumor. After trauma to the lumbar region, there is pain radiating to the lower extremities and swelling of the left leg. After CT and MRI, a large osteolytic lesion was found in the area of the sacrum and coccygeal axis.

MRI: The finding corresponds to a giant cell tumor with components of an aneurysmal bone cyst of the sacrum. There is an expansive osteolytic tumor mass with a heterogeneous signal characteristic strong in STIR and low in T1 measurements of signal intensity. Existence of so-called "fluid-fluid" levels

PET/CT/04.05.17: Soft tissue lesion in the area of the sacral bone with axial dimensions 57/49 mm and SUV max 9.2. The corticalis is destroyed both dorsally and to the pelvis.

Biopsy with pathohistological and immunohistochemical (IHC) analysis /26.04.17: Giant cell tumor of the sacrum with destructive biological behavior of borderline malignancy. There is proliferation of osteoclast-like multinuclear giant cells and polygonal, oval and drained mononuclear stromal cells with sparse cytoplasm, cytological atypism and mitotic figures. There is stromal fibrosis, osteoid formation, necrosis and hemorrhage.

Immunohistochemistry: Mononuclear tumor cells express CD99 in 90% and multinucleated CD 68 /T2N0M0 (G1-2).

CT of the pelvis/22.11.17 before radiotherapy (RT): Osteolytic and osteosclerotic lesion of the sacrum and coccygeal axis with a heterogeneous structure. Presence of a soft tissue component (Figure 1). During the month November and December 2017, a definitive intensity modulated radiotherapy (IMRT) up to total dose

(TD) 64 Gy with daily dose (DD) 2 Gy was performed (Figure 2).

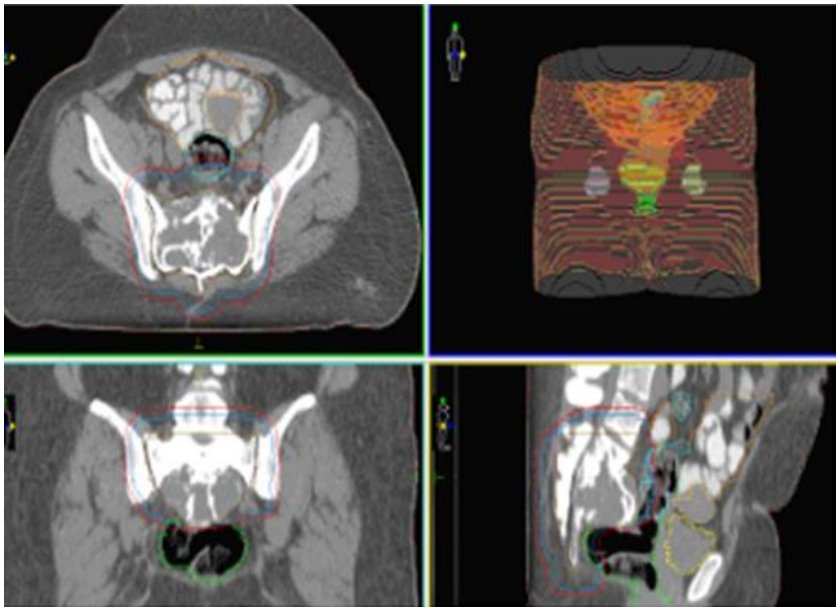

Figure 1: CT of the pelvis before radiotherapy -Osteolytic and osteosclerotic lesion of the sacrum and coccygeal axis with a heterogeneous structure. Presence of a soft tissue component.

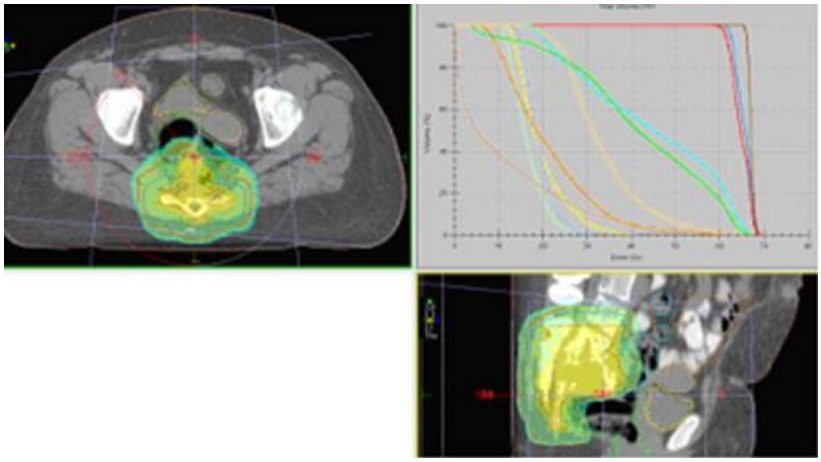

Figure 2: Definitive intensity modulated radiotherapy (IMRT) up to total dose (TD) 64 Gy with daily dose (DD) 2 Gy.

Control CT of the pelvis after 6 months from RT/15.06.18: Osteolytic and osteosclerotic lesion of sacrum and coccygeal axis with heterogeneous structure. The soft tissue lesion associated with the coccyx axis has fibrous changes. There are no enlarged lymph nodes in the small pelvis (Figure 3A). The pain syndrome has significantly decreased. Control CT of the pelvis after 1 year from RT /04.01.19- Osteolytic and osteosclerotic lesion of the sacrum. There are no enlarged lymph nodes in the small pelvis (Figure 3B).

Control pelvic CT after 2 years from RT/ 03.02. 20 (Figure /C): The pain syndrome is completely absent

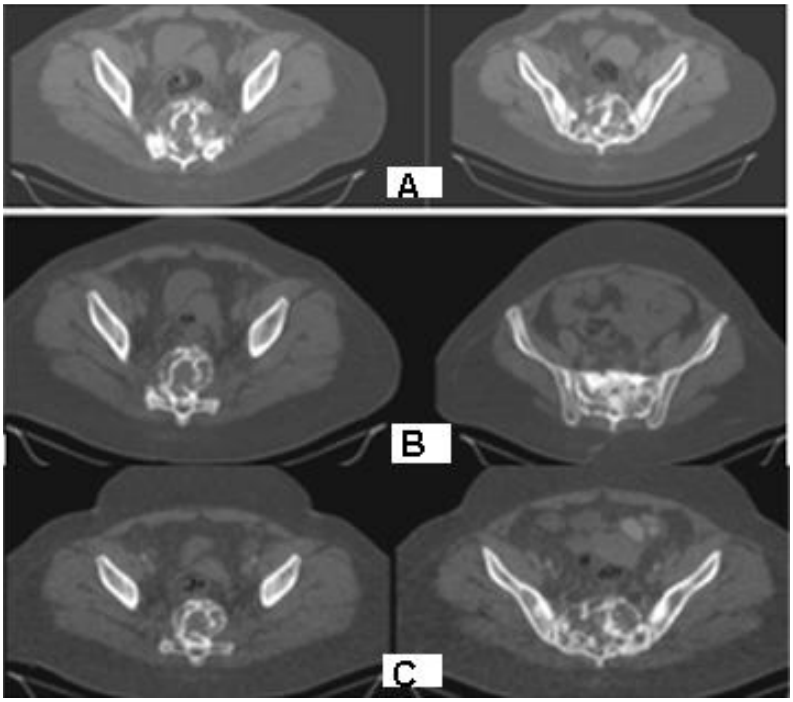

Figure 3A): CT of the pelvis after 6 months from RT-Osteolytic and osteosclerotic lesion of sacrum and coccygeal axis with heterogeneous structure. The soft tissue lesion associated with the coccyx axis has fibrous changes.; B) CT of the pelvis after 1 year from RT-Osteolytic and osteosclerotic lesion of the sacrum; C) Pelvic CT after 2 years from RT-Osteolytic and osteosclerotic lesion of the sacrum

Clinical case № 2

Since September 2022, a 13-year-old boy presented with slowly progressive low back pain that spread to the posterior surface of the right leg. The pain was hardly affected by conservative treatment. After CT and MRI imaging studies and consultation with a neurosurgeon, the child was admitted for surgical treatment.

From Spine MRI/ November 2022- Evidence of a tumor process on the right involving the body and right pedicle of the fifth lumbar vertebra (L5), exerting antero-lateral compression on the dural sac and on the nerve root at that level, with imaging features of aneurysmal bone cyst (Figure 4).

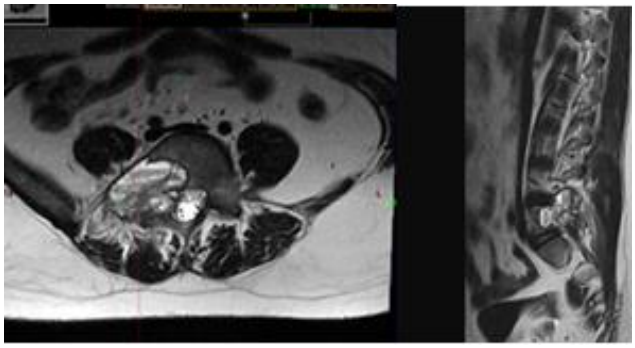

Figure 4: Spine MRI/ November 2022-Evidence of a tumor process on the right involving the body and right pedicle of the fifth lumbar vertebra (L5), exerting antero-lateral compression on the dural sac and on the nerve root at that level, with imaging features of aneurysmal bone cyst.

Intraoperative: A hemilaminectomy was performed at L5 and partial at L4. An extradural tumor formation was encountered from the body of L5 with ventral compression on the dural sac, concentrically involving the right root. The mass was soft, profusely bleeding, with the presence of multiple intradural hemorrhagic cysts and fibrous stroma at the periphery, with macroscopic features of a primary bone tumor of the body of L5. The tumor was subtotally resected, achieving wide decompression of the neural structures. Vertebroplasty of the bony tumor bed was performed.

Pathohistologicalresult-08.12.2022: Fresh hemorrhages predominate in the examined material, followed by cystic spaces without clearly formed vascular walls. In their periphery, proliferation of mesenchymal cells and clustering of osteoclast-type giant cells can be seen. Single bone lamellae are found. The lesion is partially

encapsulated. The diagnosis of aneurysmal bone cyst is confirmed. Due to the resumption of the pain syndrome, in January 2023, a follow-up MRI of the spine was performed, which established a recurrence of the disease with tumor size advancing-7.5/6/5.1 cm with compression on the spinal canal.

Conclusion: Advanced aneurysmal bone cyst at L5. Postoperative changes. Condition after L5 vertebroplasty.

Spine MRI /March 2023: The inhomogeneous mostly high-signal T1 multicystic mass involving the body of L5 on the right with the corresponding peduncle, arch and transverse process persisted. The dimensions in anterior-posterior dimension are about 6.1 cm, transverse 7.8 cm and caudal-cranial 5.1, the advancement being at the expense of the transverse dimension / towards the body medially and to the left. The stenosis of the neuroforamen on the right persists as the corticalis is not disturbed.

Conclusion: MRI data for an advancing aneurysmal bone cyst (Figure 5).

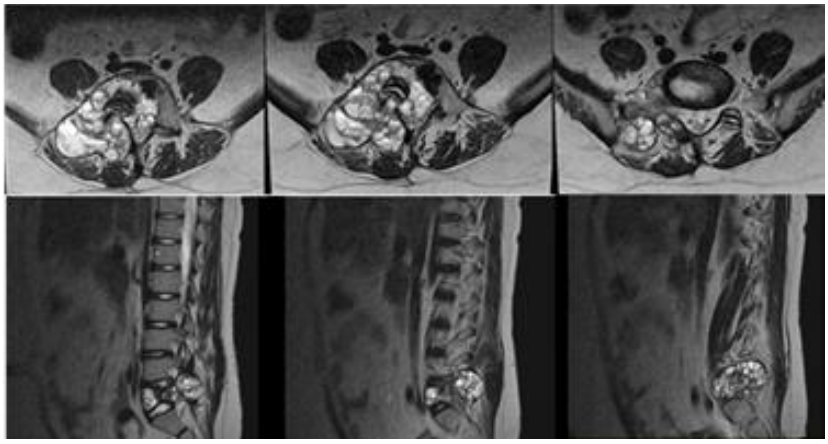

Figure 5: Spine MRI /March 2023-The inhomogeneous mostly high-signal T1 multicystic mass involving the body of L5 on the right with the corresponding peduncle, arch and transverse process persisted. The dimensions in anterior-posterior dimension are about 6.1 cm, transverse 7.8 cm and caudal-cranial 5.1, the advancement being at the expense of the transverse dimension/towards the body medially and to the left. The stenosis of the neuroforamen on the right persists as the corticalis is not disturbed.

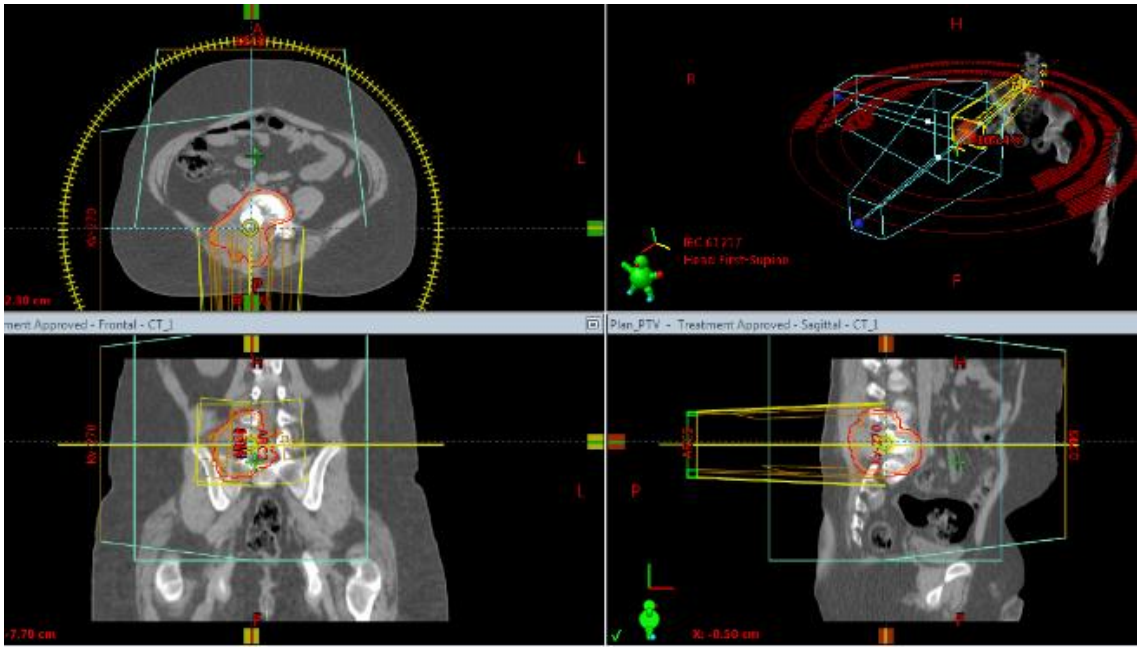

Figure 6: Intensity modulated radiotherapy (IMRT) using the VMAT method up to a total dose of 30 Gy with a daily dose of 2 Gy

Considering the benign nature of the lesion and its volume, we performed intensity modulated radiotherapy (IMRT) using the VMAT method up to a total dose of 30 Gy with a daily dose of 2 Gy (**Figure 6**). During RT, non-steroidal analgesic drugs were required, as the pain syndrome did not resolve until the RT end. 6 months after the completion of IMRT, we performed a control MRI (**Figure 7A**), which showed a significant reverse reduction of the aneurysmal bone cyst against the background of complete

anesthesia without the use of pain medication .

MRI after 1 year from IMRT: The monitored heterogeneous volumetric formation is presented without dynamics in its imaging characteristics compared to the transient MRI examination-it involves the body of the fifth lumbar vertebra, swells the right pedicle, the lamina and the facet joint" It causes stenosis of the corresponding recess and neuroforamen. The structure of the formation is heterogeneous with confluent hyperintense areas in T2 and STIR, hypointense in T1, as well as reticular osteosclerotic areas. No detectable cortical erosion. The body of the fifth lumbar vertebra is wedge-shaped in the dorsal aspect with deformation to the right. Osteosclerotic material was noted intraspongeally, presented as low signal in all dimensions **(Figure 7B)**.

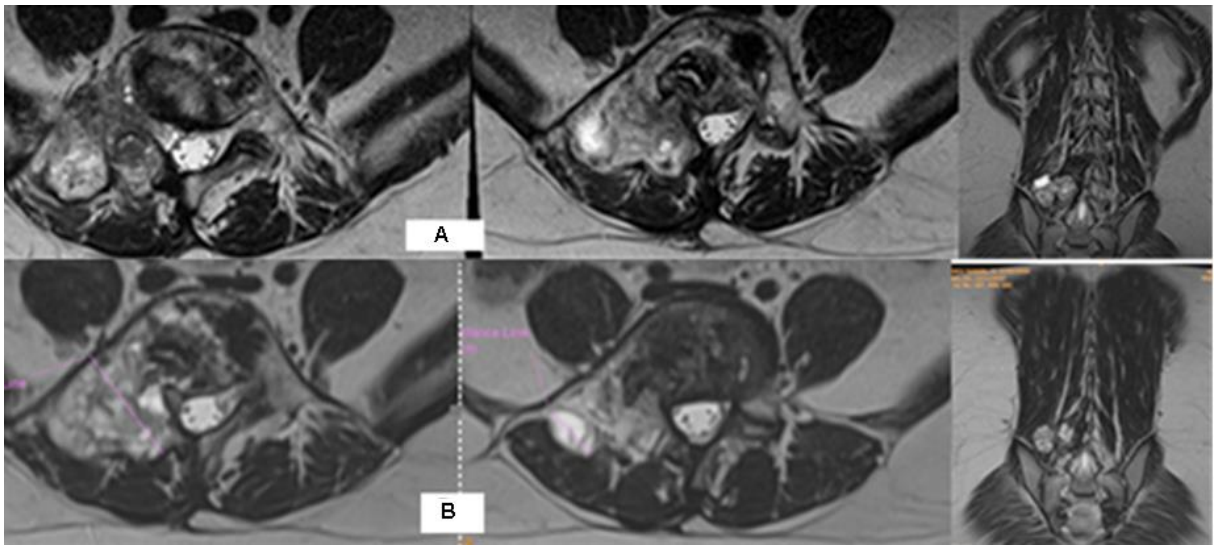

Figure 7A): MRI after 6 months from IMRT which showed a significant reverse reduction of the aneurysmal bone cyst; **B)** MRI after 9 months from IMRT-The structure of the formation is heterogeneous with confluent hyperintense areas in T2 and STIR, hypointense in T1, as well as reticular osteosclerotic areas. No detectable cortical erosion. Osteosclerotic material was noted intraspongeally, presented as low signal in all dimensions.

Discussion

Giant cell tumor of bone (GCT) is sometimes difficult to distinguish from other giant-cell-rich tumors such as aneurysmal bone cyst (ABC). Although GCT is classified as a benign neoplasm, it has a wide clinical spectrum and is similar to malignant tumors: it sometimes behaves more aggressively with a high recurrence rate and occasional metastasis to the lungs [9]. Clinically giant cell bone tumor (GCT) is usually seen as a lytic lesion of the epiphyseal bone region and most often occurs in the distal femur and proximal tibia. Radiologically usually a well-circumscribed lytic lesion over the epiphyseal region is found. Histopathologically, these tumors are comprised of mononuclear cells, macrophages and uniformly distributed multinuclear giant cells [10-12]. The mononuclear stromal cells were claimed to be the neoplastic and proliferative component of GCT's and it has been reported that these neoplastic stromal cells had been capable of inducing osteoclast-like differentiation [13-14]. The nuclei of the multinucleated giant cells were similar in size to those of the stromal cells [15]. Adjacent to the necrotic areas, mononuclear stromal cells may show cytologic atypia focally, mimicking malignancy [16]. These stromal cells may show rare mitotic figures however atypical mitosis is absent [17]. The well defined histopathologic pattern of GCT is frequently lost by secondary reactive changes such as fibro-histiocytic proliferation, hemorrhage, necrosis and aneurysmal bone cyst formation [18]. In 100% of cases with giant cell bone tumor, strong positive immunohistochemical activity to CD 68 in osteoclast-like giant cells was observed. Mean percentage positivity for CD68 (38.36%) and α1-ACT (70.86%) was higher in primary than recurrent GCT [19]. Dickson et al. and Lee et al. reported that p63 expresses in the GCT mononuclear cells and that finding was useful to distinguish GCT from other giant cell-rich tumors such as ABC and chondroblastoma [20,21].

In the general population, ABC has a predilection for children and young individuals, is diagnosed more commonly in the second decade of life and has a male to female ratio of 1:1.16 [22]. In the last WHO Classification of Tumors of Bone (2020), aneurysmal bone cysts (ABC) has been a shift in nomenclature in which the terms “ABC” and “ABC-like changes” that are found within certain preexisting primary bone neoplasms are suggested instead of “primary ABC” and “secondary ABC,” respectively [23]. They are usually expansive blood-filled cavities within the bone lined by proliferative fibroblasts, giant cells, and trabecular bone [24]. The majority of ABCs are primary, and some are secondary, but both primary and secondary ABCs can develop into osteosarcoma, and certain benign or malignant tumors may be combined with ABCs [25]. Aneurysmal bone cyst (ABC) is made up of several cystic cavities which contain uncongealable blood. The individual cystic cavities are separated by septa, which are composed of fibrous tissues, blood capillaries and giant cells [26,27]. In ABC, giant cells are smaller and giant cells are unevenly distributed. In solid type of ABC, stroma is more fibrotic than that of GCT [28].

However, the pathogenesis of ABC arising from GCT remains unclear. The hemodynamic changes caused by the fistula lead to vasodilation and bone destruction, resulting in the formation of ABC [29]. In the two clinical cases presented, we report a typical histopathological finding corresponding to these two rare osteoclastic benign tumors. Giant cell tumor of the sacrum shows destructive biological behavior of borderline malignancy. It is represented by a proliferation of osteoclast-like multinucleated giant cells and polygonal, oval, and drained mononuclear stromal cells with scant cytoplasm, cytological atypism, and mitotic figures, as well as stromal fibrosis, osteoid formation, necrosis, and hemorrhage. Mononuclear tumor cells express CD99 in 90% and multinucleated CD 68, which proves the diagnosis GCT. In the examined material of the aneurysmal bone cyst, fresh hemorrhages predominate, followed by cystic spaces without clearly formed vascular walls. In their periphery, proliferation of mesenchymal cells and clustering of osteoclastic-type giant cells can be seen. Single bony lamellae occur. The lesion is partially encapsulated. The most differential radiological GCT characteristics are multiple anomalous branches in angiogram, multilocular cystic structure in the Computed Tomography (CT) with bone window, presence of liquid both in the CT or Magnetic Resonance Imaging (MRI) [30]. The presence of calcified shadows in the lesion and sclerosing edges could also suggest that the lesion is ABC secondary to GCT, since such changes are also absent in simple GCT [31,32].

The typical radiographic appearance of aneurysmal bone cyst is that of an eccentric, lytic, geographical, metaphyseal lesion with a sclerotic border with or without septations [33].On MRI, ABC lesions were characterized by enlarged masses with lobulated outer margins. The lesions were also found to have low signal intervals on both T1WI and T2WI. The fluid in the cystic cavity showed uneven low or medium-high signal on T1WI sequence and an uneven high signal on T2WI [15].

Imaging of the aneurysmal bone cyst presents a tumor with sharp contours and a characteristic multicystic septate structure with formed fluid-fluid levels. It causes ventral and lateral stenosis of the spinal canal with dural compression and obliterates the corresponding root canal (Figure 4, 5 and 7). In giant cell bone tumor, it is observed clearly visible expansive osteolytic tumor mass with a heterogeneous signal characteristic strong in STIR and low in T1 measurements of signal intensity, as well as the presence of the so-called “fluid-fluid” levels (Figure 1 and 3).

Indications for the Use of Radiation Therapy in Giant Cell Bone Tumor

Radiation therapy is not routinely used, due to an increased risk of secondary neoplasms in young people, as well as the risk of sarcoma cell transformation of this borderline tumor [34]. Indications for radiotherapy are tumors with pathohistologically undifferen-tiated, rapidly dividing tumor cells, tumor recurrences without RT performed, mainly tumors with pelvic and cranial localization and at risk of extended surgical interventions due to unacceptable postoperative deformities [35-40].

RT is imposed as adjuvant therapy after nonradical surgery or as alternative treatment for inoperible tumors, as well as in tumors with certain local disadvantages of functional deficiency after surgery [41,42]. Local recurrences after a single RT reached 49%, after surgery with positive resection lines -47%, after a positive resection lines surgery followed by RT-46% and 0% after a radical operation [43]. GCTs offers a very large range of realized doses up to 35-54-64Gy through conventionally fractionated RT [37,44]. After RT up to TD 40-60 Gy realized with 15-30 fractions for a period of 3-6 weeks, 90% local tumor control (LTC) was achieved [42.45]. In GCTs less than 4 cm in diameter after single RT up to TD 40-45Gy 90% LTC is reported, and in larger ones recommended a combination of the surgery and RT [46]. 3D conformal RT and IMRT are possible to realize high radiation doses to increase LTC without significant late radiation changes in the adjacent healthy tissues. In the presented clinical case with the inoperable sacral giant cell tumor, we performed definitive intensity modulated radiotherapy using the VMAT method up to total dose (TD) 64 Gy with daily dose (DD) 2 Gy (Figure 2).

Indications for the Use of Radiation Therapy in ABC

Radiotherapy is an option currently reserved for patients at high risk of not withstanding surgery or for those who are resistant to surgical treatment, even more so considering the potential risks of post-radiation myelopathy or sarcomatous transformation [47]. Five German institutions collected data regarding clinical features, treatment concepts, and outcome for patients with ABC who had been referred for local external beam radiotherapy (EBRT) over the past 30 years. All 7 patients exhibited a radiological response and experienced no recurrent disease activity or pain during follow-up [48]. Radiotherapy seems to be effective for recurrent cases of ABC and a dose of around 25 to 36 Gy could be effectively delivered with satisfactory results [49,50]. In the presented clinical case with the recurrent aneurysmal bone cyst, we performed definitive intensity modulated radiotherapy using the VMAT method up to total dose (TD) 30 Gy with daily dose (DD) 2 Gy (Figure 6).

Conclusion

Giant cell tumor of bone and aneurysmal bone cyst are rarely diagnosed osteoclastic benign tumors. A strict histopathological diagnosis is required, which determines the necessary therapeutic behavior. Imaging / CT and MRI support the differential diagnosis and biological behavior of each of the above-mentioned tumors. Due to the fact that they are benign tumors, the main treatment is radical surgery. Indications for radiotherapy are giant cell tumors with pathohistologically undifferentiated, rapidly dividing tumor cells, tumor recurrences, mainly tumors with pelvic and cranial localization and at risk of extended surgical interventions. To achieve 90% local tumor control in GCT, high radical doses of 40-60 Gy are required. In the aneurysmal bone cyst, it is necessary to implement low radiation doses of 25-36 Gy, due to the risk of developing a secondary radiation-induced tumor. In case of recurrent and inoperable spinal ABC, despite the benign nature of the disease and the child's and adolescent age, external beam radiotherapy is required. IMRT up to a total dose of 30 Gy achieves significant tumor reduction with complete analgesia and absence

of neurological symptoms. In both tumors, our observations show that on the 6th month after IMRT, a sclerosing effect in the bony spongiosa was observed, clearly visible on the control CT and MRI, as well as a complete impact on the pain syndrome.

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