CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

A rare tumor in a rare location: giant cell tumor of the sacrum and ilium – case report and current perspectives

ALEXANDRU POLL[1)], VANDA ROXANA NIMIGEAN[2)], MARIA JUSTINA ROXANA VÎRLAN[2)], VALENTIN DANIEL SÎRBU[3)], MARIANA COSTACHE[4)], ROXANA VICTORIA IVAŞCU[1)], MARIANA CORDUN[5)], VICTOR NIMIGEAN[1)]

[1)]*Department of Anatomy, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[2)]*Department of Oral Rehabilitation, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[3)]*Department of Implant Prosthetic Therapy, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[4)]*Department of Pathology, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[5)]*Department of Special Motricity and Medical Recovery/Rehabilitation, Faculty of Kinetotherapy, National University of Physical Education and Sport, Bucharest, Romania*

Abstract

Giant cell tumor (GCT) is considered a locally aggressive, intermediate grade benign bone neoplasm. In rare cases, GCT undergoes malignant degeneration or may cause distant metastasis, mainly in the pulmonary area. Most bone GCTs are situated in the epiphysis or metaphysis of long bones, while GCTs of the pelvis are quite rare. There is no standard treatment protocol for the GCT of pelvic bones. This paper presents the therapeutic management of a rare case of a stage III GCT, situated on the iliac tuberosity, sacral wing and partially the left iliac wing. The chosen treatment consisted in intralesional curettage, high-speed burring, phenolization and hydrogen peroxide lavage. At the six-week follow-up, the patient reported minimal disability. No complications and no local infections were revealed. Healing was confirmed by the two-year postoperative follow-up. This case report demonstrates that intralesional curettage complemented with adjuvant therapies is a viable alternative to wide resection surgery for the treatment of aggressive GCT.

Keywords: giant cell tumor, pelvis, stage III, immunohistochemistry, intralesional curettage, adjuvant therapies.

Introduction

Giant cell tumor (GCT) is considered a locally aggressive, intermediate grade benign bone neoplasm [1–4]. This slow-growing tumor may lead to pathological fractures and/or postoperative infections [5, 6]. In rare cases, GCT undergoes malignant degeneration [6] or may cause distant metastasis, mainly in the pulmonary area [3, 5–9].

GCT usually affects adults, with a slight predominance for females, and its mean age of onset is in the third decade of life [3, 4, 10–14]. However, GCT can also be encountered in a very small proportion in the pediatric population [8].

Most bone GCTs are situated in the epiphysis or metaphysis of long bones, such as distal femur, proximal tibia, distal radius, proximal femur and proximal humerus [1, 4, 12, 15, 16]. However, GCT can also develop in the pelvic bones [14]. The incidence of GCT in the ilium and ischium bones is extremely low [17].

Histologically, GCT contains elongated, round or oval mononuclear cells and characteristic multinucleated osteoclast-like giant cells that express receptor activator of nuclear factor-*kappa* B (RANK) [1, 5, 6, 18]. Very important is the fact that RANK ligand (RANKL) is considered a mediator of osteoclast activation [1]. Radiologically, GCT presents well-defined radiographic margins [5].

The treatment options for bone GCTs are very diverse, for example: aggressive curettage, cement filling and oral bisphosphonates [19], en bloc resection followed by bulk allograft or prosthetic reconstruction [12], Denosumab administration [1, 20–22], arterial embolization [9, 23, 24], radiotherapy [25], intralesional curettage [26] or wide resection [27, 28]. However, concerning the pelvis GCT, there is no standard treatment protocol in the medical guidelines [28].

This paper presents the therapeutic management of a rare case of pelvic GCT, situated on the iliac tuberosity, sacral wing and partially the left iliac wing. The chosen treatment consisted in intralesional curettage, high-speed burring, phenolization and hydrogen peroxide lavage. Healing was confirmed by the two-year follow-up. This case report demonstrates that, in case of pelvic GCT stage III – aggressive tumor, complete healing may be achieved with intralesional curettage, high-speed burring, phenolization and hydrogen peroxide, without the need of wide resection surgical techniques.

Case presentation

A 52-year-old woman presented to an orthopedic medical center complaining of pain in the left gluteal region, left intermittent sciatic nerve pain and irradiated pain in the lumbar and left paravertebral regions. The physical examination revealed moderate enlargement of the left gluteal region. Moreover, on palpation, an

immovable and painful mass could be felt. The radiographic analysis showed an image of osteolysis with relatively well-defined margins (known as 'puddle on the sand') on the left iliac wing (Figure 1).

Afterwards, more complementary investigations were recommended: pelvic and pulmonary computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) of the pelvis. The pelvic CT examination revealed an isodense lesion that affected the iliac tuberosity, the left iliac wing and the left sacral wing towards the conjugate sacral foramina S1–S2. Small protrusions of the lesion into the trabecular bone and contiguity of the cortical bone at the level of the conjugate sacral foramina S1–S2 could also be observed (Figure 2, a and b).

The pulmonary CT did not show any lung tissue modification. MRI examination showed high signal intensity on T1-weighted images and inhomogeneous low signal intensity on T2-weighted images, with location on the iliac tuberosity, iliac and sacral wings, without interfering with the sacral nerve roots (Figures 3–5).

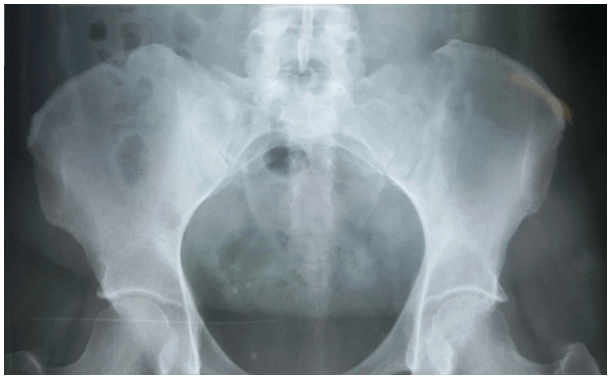

Figure 1 – ***Preoperative anteroposterior pelvic radiograph. Osteolysis areas with 'soap bubbles' appearance, situated at the level of the iliac tuberosity and iliac wing can be observed.***

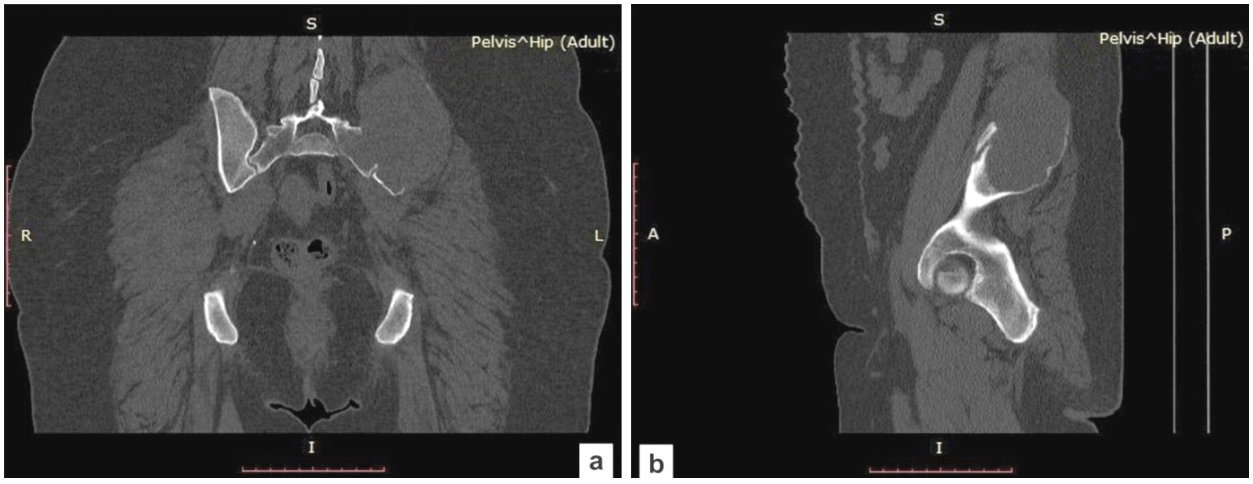

Figure 2 – ***Computed tomography (CT) images: (a) Coronal view; (b) Sagittal view. An isodense tumor presenting expansion, thinning or even disappearance of the posterior cortical can be seen. The extension of the tumor into the adjacent soft parts can also be observed.***

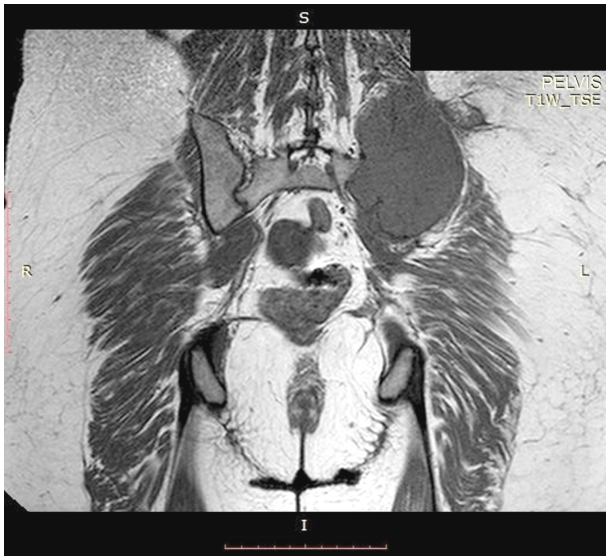

Figure 3 – ***Preoperative contrast-enhanced coronal T1W image of MRI. Tumor in hypersignal, located in the iliac tuberosity, the iliac wing and the sacral wing. Tumor extension into the adjacent soft parts can be observed. MRI: Magnetic resonance imaging; T1W: T1-weighted; TSE: Turbo spin echo.***

Following these investigations, the incisional biopsy was performed, and the tumoral tissue fragments were sent to the histopathological (HP) examination. Macroscopically, the tumoral tissue looked as a meaty reddish-purple tissue of soft consistency. The HP diagnosis was GCT (Figures 6–10).

Surgical treatment was decided upon. Regarding the clinical stadialization of the tumor, the given case was a stage III – aggressive tumor, according to the grading system described by Campanacci *et al.* [29]. The tumor was located in the type I surgical area, defined by Enneking & Dunham [30].

The surgical approach began with an "omega" incision, which followed the iliac crest and went up paravertebrally to the left, because of the tumor extension into the soft tissues of the area. The surgical treatment consisted not only in intralesional curettage but also in high-speed burring, phenolization and hydrogen peroxide lavage. High-speed burring was used especially for the tumoral margins. Acrylic cement was not applied, mainly because the thermal effect generated by the polymerization of the cement could have caused a lesion to the nerve roots, which were situated in the proximity of the tumor site.

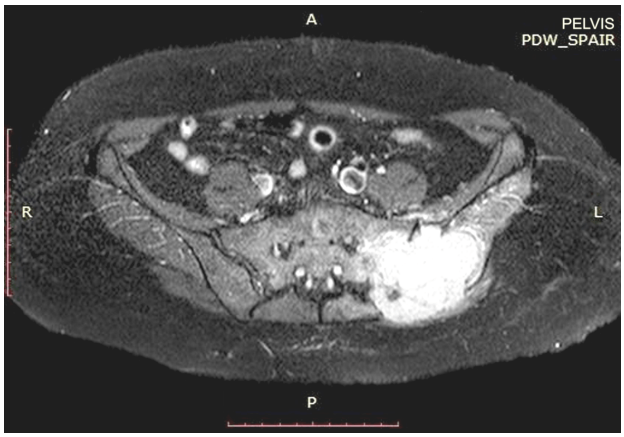

Figure 4 – ***Preoperative contrast-enhanced fat suppressed axial PDW–SPAIR image of MRI. Tumor in hypersignal. MRI: Magnetic resonance imaging; PDW: Proton density weighted; SPAIR: Spectral attenuated inversion recovery.***

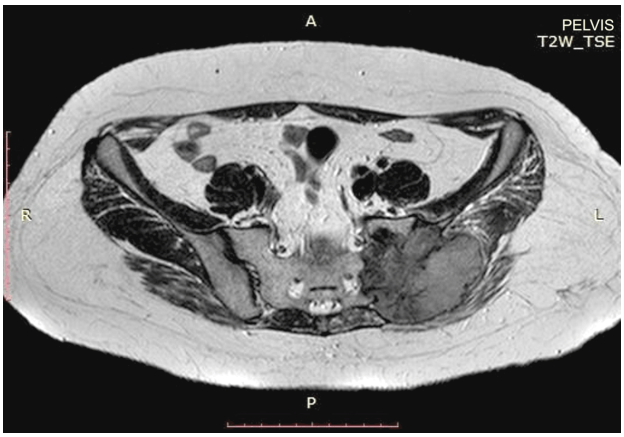

Figure 5 – ***Preoperative contrast-enhanced axial T2W image of MRI. The image shows the tumor with inhomogeneous hyposignal located in the iliac tuberosity, iliac wing and the sacral wing, without affecting the conjugate sacral foramina. MRI: Magnetic resonance imaging; T2W: T2-weighted; TSE: Turbo spin echo.***

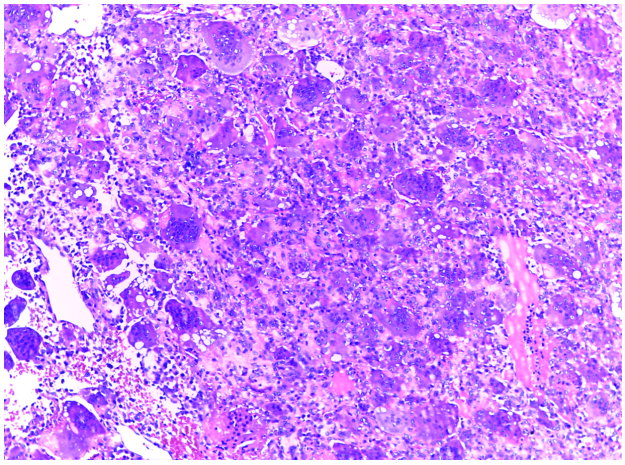

Figure 6 – ***Multinucleated giant cell tumor of bone. Numerous large osteoclast-like cells can be observed. The cells present nuclei arranged on the entire surface of the cell and are located in an inflammatory stroma with congestive blood vessels. HE staining, ×100. HE: Hematoxylin–Eosin.***

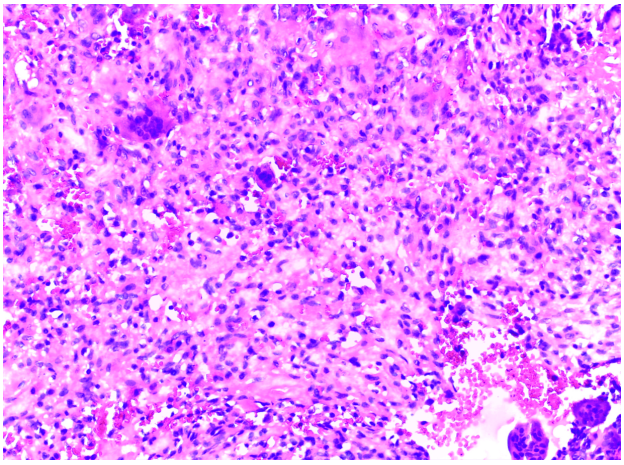

Figure 7 – ***Multinucleated giant cell tumor of bone. The giant multinucleated cells present eosinophilic cytoplasm and central basophilic nuclei. The fibrous stroma exhibits mixed inflammation and blood vessels hyperemia. HE staining, ×200. HE: Hematoxylin–Eosin.***

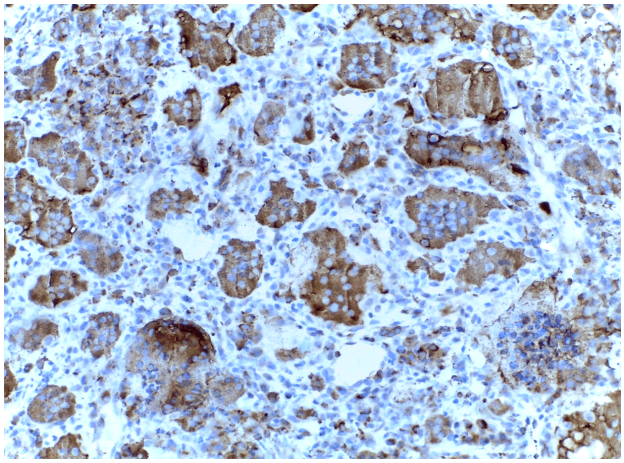

Figure 8 – ***Multinucleated giant cell tumor of bone. IHC staining with multinucleated giant cells displaying cytoplasmic positivity for CD68; rare macrophages can also be seen. Anti-CD68 antibody immunomarking, ×200. IHC: Immunohistochemical; CD68: Cluster of differentiation 68.***

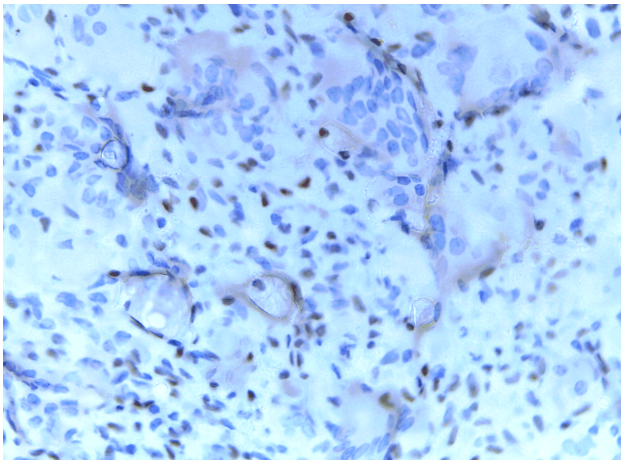

Figure 9 – ***Multinucleated giant cell tumor of bone: IHC staining; p63 was found positive intranuclear in the rare inflammatory cells and negative in the multinucleated giant cells. Anti-p63 antibody immunomarking, ×400. IHC: Immunohistochemical.***

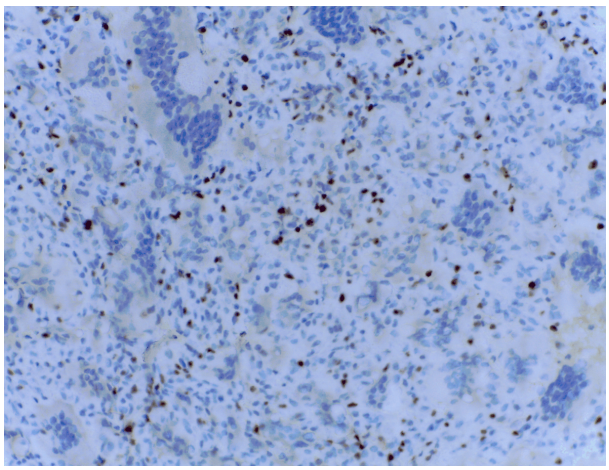

Figure 10 – ***Multinucleated giant cell tumor of bone: IHC staining with inflammatory cells intranuclear positivity for Ki-67; the multinucleated giant cells are Ki-67 negative. Anti-Ki-67 antibody immunomarking, ×200. IHC: Immunohistochemical.***

The surgical intervention was extended 2 cm from the tumor margins into the soft tissues (Figures 11 and 12). The line of the initial biopsy was resected as well. At the end, a prophylactic iliolumbar stabilization using the CD Horizon Legacy Spinal System (Medtronic instruments) was performed (Figure 13).

The postoperative evolution was favorable: the patient was given anti-inflammatory medication, painkillers, antibiotics and anti-clotting agents. No weight bearing was recommended for about five weeks, aiming to protect the osteosynthesis assembly and to favor the healing of the surgical wound. Denosumab was administered for six months postoperatively.

Follow-up information was obtained during regular examinations using the Oswestry Low Back Disability Questionnaire, complications assessment and local infections control. At six weeks, the Oswestry Low Back Disability Questionnaire showed a 15% score, which means minimal disability. No postoperative complications and no local infections were revealed. The physical examination showed good local and general conditions and favorable evolution. At two-year follow-up, patient-reported and objective findings revealed good surgical outcomes and normal lower limb function. The local disease control was performed by MRI investigation, which revealed no signs of local recurrence (Figures 14–18). A fibrosis area on the left iliac wing could be observed on MRI images.

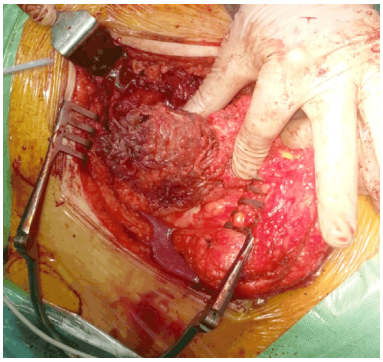

Figure 11 – ***Intraoperative appearance of the tumor prior to treatment. The dark purple color of the tumor compared to the surrounding tissues can be observed.***

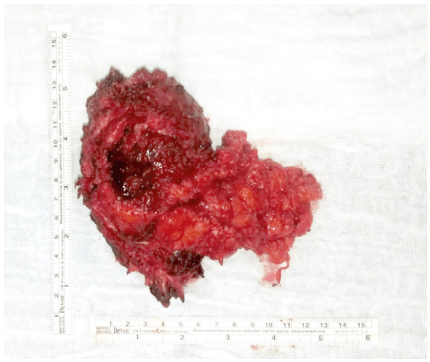

Figure 12 – ***The macroscopic aspect of the surgically removed piece.***

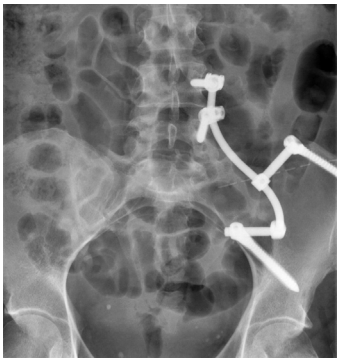

Figure 13 – ***Postoperative anteroposterior radiograph. The CD Horizon Legacy Spinal System with two transpedicular vertebral screws at the L4 and L5 level, two iliac (supra-acetabular and iliac) fixation screws and a stabilizer bar can be seen on the radiograph.***

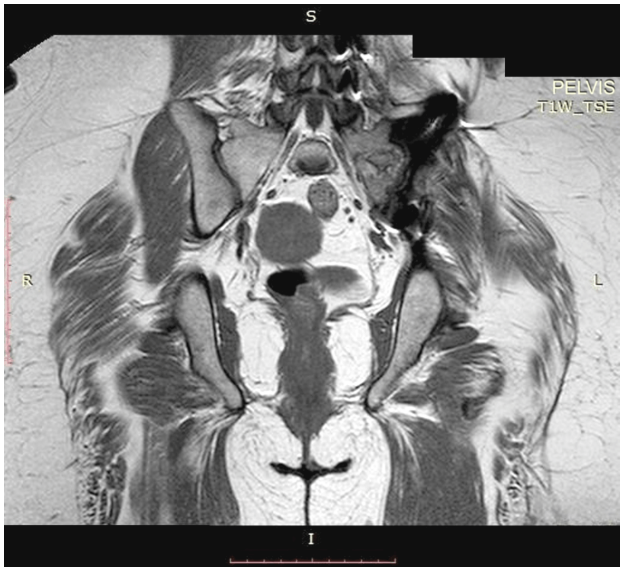

Figure 14 – ***Two-year follow-up contrast-enhanced coronal T1W image of MRI. The postoperative area presents hyposignal on T1W sequence. The postoperative area, situated in the proximity of the left conjugated foramina S1–S2, has poly-lobular appearance and dimensions 30/16/23 mm (CC/AP/T – Craniocaudal/Anteroposterior/Transversal). MRI: Magnetic resonance imaging; T1W: T1-weighted; TSE: Turbo spin echo.***

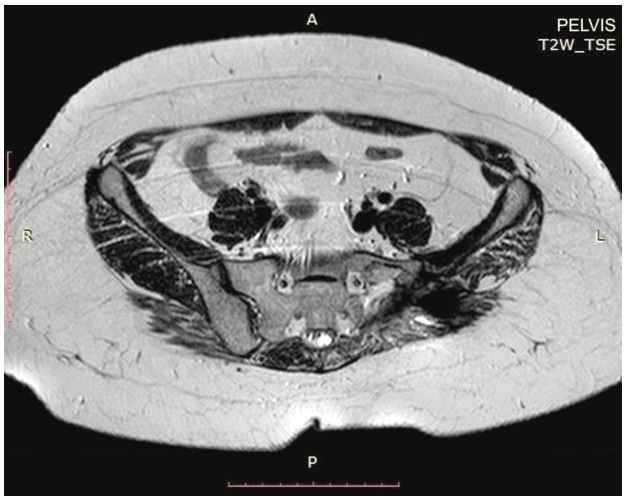

Figure 15 – ***Two-year follow-up contrast-enhanced axial T2W image of MRI. Hypersignal in the postoperative area can be observed on T2W sequence. MRI: Magnetic resonance imaging; T2W: T2-weighted; TSE: Turbo spin echo.***

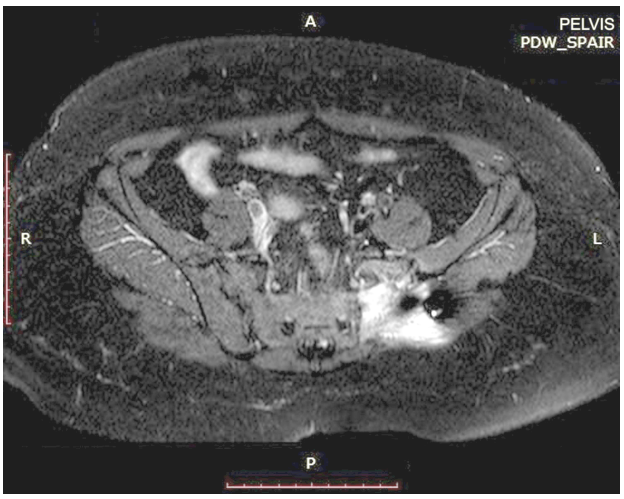

Figure 16 – ***Two-year follow-up contrast-enhanced axial fat suppressed PDW–SPAIR image of MRI. Post-operative hypersignal can be noticed. MRI: Magnetic resonance imaging; PDW: Proton density weighted; SPAIR: Spectral attenuated inversion recovery.***

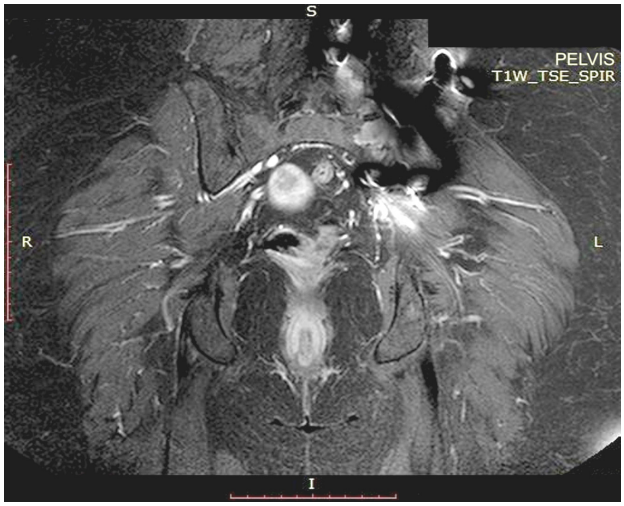

Figure 17 – ***Two-year follow-up contrast-enhanced coronal T1W image of MRI. Signal intensification on the periphery of the postoperative area can be observed. If it had been tumor recurrence, then the signal intensification would have been in the whole area, and not only on the periphery. MRI: Magnetic resonance imaging; SPIR: Spectral presaturation with inversion recovery; T1W: T1-weighted; TSE: Turbo spin echo.***

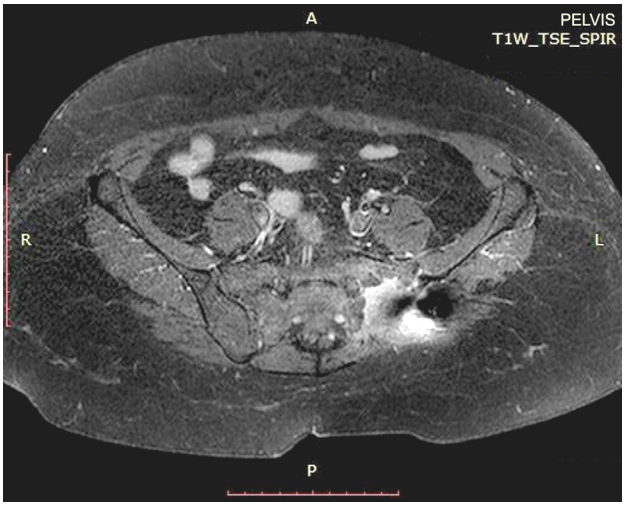

Figure 18 – ***Two-year follow-up contrast-enhanced axial T1W image of MRI. Signal intensification on the periphery of the postoperative area. Fibrous tissue appearance in the bone resection area can be observed. MRI: Magnetic resonance imaging; SPIR: Spectral presaturation with inversion recovery; T1W: T1-weighted; TSE: Turbo spin echo.***

Discussions

GCT is a primary bone tumor characterized by mononucleated cells and osteoclast-like multinucleated giant cells [24]. The resorptive giant cells are formed as a result of the fusion between stromal cells and monocytes [31, 32]. From the morphological point of view, it can be difficult to differentiate giant cell lesions by common histological methods [33]. Therefore, in the present study, the GCT diagnosis was confirmed by corroborating information from the clinical, MRI, CT and HP examinations. Moreover, several immunohistochemical markers were detected: cluster of differentiation 68 (CD68), p63 and Ki-67. CD68 is a monocyte–macrophage lineage marker, which has been linked with giant cells [31, 33, 34], while p63 expression in GCT is higher than in other giant cell-rich tumors [35–37]. Also, the Ki-67 antigen is a human nuclear protein known as a cellular proliferation marker [38, 39]. The immunohistochemistry analysis showed that the mononuclear tumor cells displayed intranuclear positivity for Ki-67 (Figure 9), revealing the fact that the GCT investigated in this case was an aggressive type of tumor.

There is no agreement regarding the therapeutic management of GCTs of rare localizations, as these tumors are usually asymptomatic in the early stages, can become very large and vascular and can grow in the proximity of the nerve roots [24, 40–42]. Therefore, the chosen treatment should aim to preserve the nerve function [24], cause minimal disability and complications to the patient without increasing the risk of tumor recurrence. Several therapies have been used for the management of

pelvic GCTs, but the surgical treatment is mostly preferred. The local recurrence rate mainly depends on the type of the surgical treatment performed [43]. The surgical approaches encountered in the literature vary between intralesional curettage supplemented with different adjuvant local treatments and wide resection techniques [28, 43]. Some research groups concluded that simple intralesional surgery is prone to a relatively high recurrence rate [19]. Therefore, simple curettage has been replaced by aggressive intralesional curettage, described as a technique in which the affected bone is ground with a high-speed burr, washed under pulse pressure and treated with different additional substances [19]. However, the recurrence rates are considered to be lower with wide resection [43]. Nevertheless, wide resection presents several disadvantages including prolonged operative time, higher risk of infection and possible nerve injury, as well as the need of a complex reconstruction of the hip with prosthesis or allograft [19, 28]. Therefore, it is difficult to achieve an ideal balance between the need to completely remove the tumor with no local and distal recurrences and the objective of improving the quality of life of the patient by keeping most of the nearby vascular and nerve tissues [44].

According to a 2008 study by Balke *et al.*, the combination of intralesional curettage with local adjuvant therapies (bone cement, burring and hydrogen peroxide) reduces the risk of tumor recurrence by 28.2%, compared to curettage only and therefore it should be considered the standard treatment [45].

Lim & Tan, in 2005, noted that the use of complementary therapy like phenol or liquid nitrogen seems to lower the risk of GCT recurrence after intralesional curettage [46]. A later literature review found that adjuvants, such as phenol, do not contribute to the lowering of the recurrence rates of GCT following intralesional management [47]. The authors of the review concluded that the most important step in GCT treatment, which results in lower recurrence of the tumor, consists in a meticulous surgical technique (intralesional curettage) complemented with high-speed burring [47].

Li *et al.*, in 2016, illustrated that, compared to curettage and wide resection, extensive curettage provides the favorable local control and functional recovery [48].

In the present case, the chosen treatment consisted in intralesional curettage and adjuvant therapies (high-speed burring, phenolization, hydrogen peroxide lavage) that lead to a fast recovery of the patient, preservation of the functions and no local recurrence at the two-year follow-up. Our results are in line with other research papers on this subject.

Giant cells in GCT express RANKL, which is responsible for the formation of osteoclastic cells and the osteolytic nature of GCT [21, 22, 49]. Denosumab is a fully humanized monoclonal antibody, which can combine with RANKL specifically and block RANKL–RANK pathway [49–51]. Therefore, Denosumab can inhibit osteoclast-like giant cells' differentiation and block normal and neoplastic osteolysis [22, 49, 50, 52, 53]. Denosumab is currently approved by the Food and Drug Administration (FDA) for the treatment of aggressive GCT of bone in adults and skeletally mature adolescents [49, 51, 54, 55]. Some authors stated that Denosumab should be the first-line therapeutic option for patients with inoperable or metastatic GCT [49, 55]. Moreover, another research group recommended the use of Denosumab, together with other treatments, in all recurrent GCTs, in grade II lesions with high surgical risk, metastatic lesions and grade III lesions [21]. Several studies concluded that the use of Denosumab, alone or as a neoadjuvant therapy for the treatment of GCT leads to clinical benefits [21, 49, 51, 53, 56, 57]. Moreover, it was suggested that Denosumab can reduce the tumor size, thus reducing the intraoperative blood loss and facilitating the surgical intervention [50, 51, 57]. However, the recent study (2018) by Yang *et al.* concluded that because of the resulted higher sclerosis and bony separation, the surgery might be more difficult [50]. As well, other authors concluded that the timing of use of neoadjuvant therapy in locally advanced Campanacci grade 3 tumors is still under debate [49]. In our study, due to the large size of the tumor, it was decided that surgical intervention should be carried out immediately. Treatment with Denosumab was subsequently recommended by the oncologist.

One of the limitations of this study is the fact that the last considered follow-up was at two years after surgery. However, a group of researchers stated that 70% of local recurrences occur within the first two years [28, 58]. Therefore, the two-year follow-up can give us viable data about the positive healing with no recurrence in the presented case.

Conclusions

In the present case of stage III iliosacral GCT, with invasion of the sacral foramina, the surgical treatment chosen (intralesional curettage, high-speed burring for the margins, phenolization and local hydrogen peroxide application) lead to complete healing at the two-year follow-up. No complications and no local infections were revealed and the limb functions were almost completely restored. Intralesional curettage and adjuvant therapies (high-speed burring, phenolization and local hydrogen peroxide lavage) are a viable alternative to wide resection methods for the treatment of pelvic GCTs.

Compliance with ethical standards

Informed consent in written form was obtained from the patient for publishing this case report.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Alexandru Poll and Maria Justina Roxana Vîrlan have equal contributions to this paper and thus are main authors.

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Corresponding author
Vanda Roxana Nimigean, Associate Professor, DMD, PhD, Head of Oral Rehabilitation Department, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, 17–23 Plevnei Avenue, Sector 6, 060015 Bucharest, Romania; Phone +40721–561 848, e-mail: vandanimigean@yahoo.com

Received: February 17, 2019

Accepted: November 25, 2019