Review Article
Tumor/Infection
http://dx.doi.org/10.1590/S1808-185120252403299470

PRIMARY ANEURYSMAL BONE CYST OF THE SPINE: DIAGNOSIS AND THERAPEUTIC ALTERNATIVES FROM PHARMACOLOGICAL TO SURGICAL MANAGEMENT - REVIEW ARTICLE

CISTO ÓSSEO ANEURISMÁTICO PRIMÁRIO DA COLUNA VERTEBRAL: DIAGNÓSTICO E ALTERNATIVAS TERAPÊUTICAS DO MANEJO FARMACOLÓGICO AO CIRÚRGICO – ARTIGO DE REVISÃO

QUISTE ÓSEO ANEURISMÁTICO PRIMARIO DE LA COLUMNA VERTEBRAL: DIAGNÓSTICO Y ALTERNATIVAS TERAPÉUTICAS DESDE EL MANEJO FARMACOLÓGICO HASTA EL QUIRÚRGICO – ARTÍCULO DE REVISIÓN

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ABSTRACT

Aneurysmal bone cyst (ABC) is a benign, rare, and potentially aggressive neoplasm that may affect the spine and pose significant therapeutic challenges, particularly in this location. Although surgical resection has historically been the mainstay of treatment, recent advances in pharmacological and minimally invasive strategies – such as embolization, sclerotherapy, and intralesional injections – have expanded the therapeutic alternatives. Traditional surgical methods are associated with high recurrence rates and significant morbidity, especially when the spine is involved. This review synthesizes the current knowledge regarding pathophysiology, diagnostic methods, and the spectrum of therapeutic modalities, emphasizing the role of minimally invasive techniques for spinal ABCs. ***Level of Evidence IIIb; Review Article.***

Keywords: Bone Cysts; Spine; Bone Tumor.

RESUMO

O cisto ósseo aneurismático (COA) é uma neoplasia benigna, rara e potencialmente agressiva, que pode afetar a coluna vertebral e representa desafios terapêuticos significativos, especialmente nessa localização. Embora a ressecção cirúrgica tenha sido historicamente a base do tratamento, avanços recentes em estratégias farmacológicas e minimamente invasivas – como embolização, escleroterapia e injeções intralesionais – ampliaram as alternativas terapêuticas. Métodos cirúrgicos tradicionais estão associados a altas taxas de recorrência e morbidade significativa, especialmente quando a coluna está envolvida. Esta revisão sintetiza o conhecimento atual sobre a fisiopatologia, os métodos diagnósticos e o espectro das modalidades terapêuticas, com ênfase no papel das técnicas minimamente invasivas para o tratamento do COA espinal. ***Nível de Evidência IIIb; Artigo de Revisão.***

Descritores: *Cisto Ósseo; Coluna Vertebral; Tumor Ósseo.*

RESUMEN

El quiste óseo aneurismático (QOA) es una neoplasia benigna, rara y potencialmente agresiva que puede afectar la columna vertebral y plantea importantes desafíos terapéuticos, particularmente en esta localización. Aunque la resección quirúrgica ha sido históricamente el pilar del tratamiento, los avances recientes en estrategias farmacológicas y mínimamente invasivas – como la embolización, la escleroterapia y las inyecciones intralesionales – han ampliado las alternativas terapéuticas. Los métodos quirúrgicos tradicionales están asociados con altas tasas de recurrencia y morbilidad significativa, especialmente cuando está involucrada la columna vertebral. Esta revisión sintetiza el conocimiento actual sobre la fisiopatología, los métodos diagnósticos y el espectro de modalidades terapéuticas, con énfasis en el papel de las técnicas mínimamente invasivas para el QOA espinal. ***Nivel de Evidencia IIIb; Artículo de Revisión.***

Descriptores: *Quiste Óseo; Columna Vertebral; Tumor Óseo.*

Definition

Aneurysmal bone cyst (ABC) is a benign neoplasm characterized by rapid and locally destructive growth, first described by Jaffe and Lichtenstein in 1942, when the authors observed pelvic and spinal lesions in which surgical incision of the thin wall revealed a large cavity filled with abundant bloody fluid.[1]

The World Health Organization classifies ABC as a bone tumor of uncertain neoplastic nature and defines it as a benign cystic bone

Study conducted by the
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Received on 08/01/2025 accepted on 08/18/2025
Reviewed by: Helton Delfino

lesion composed of blood-filled cavities separated by connective tissue septa containing fibroblasts, osteoclast-like multinucleated giant cells, and reactive bone tissue.[2]

ABC may arise *de novo* (primary) or develop secondarily in association with other benign or malignant bone tumors that undergo hemorrhagic cystic degeneration.[3] Primary ABC accounts for approximately 70% of all cases and are more prevalent in the pediatric population.[4] The remaining 30% most frequently occur in adults secondary to degenerative hemorrhagic events in pre-existing tumors, such as giant cell tumor, chondroblastoma, non-ossifying fibroma, osteoblastoma, osteosarcoma.[3]

Epidemiology

ABC accounts for approximately 1% of all bone tumors and are more common within the first two decades of life with a slight female predominance.[2] The most frequent locations include distal femur and proximal tibia metaphyses.[4] In an epidemiological review of 411 children with ABCs, the spine (14.7%) was the third most common location, after the femur (22.3%) and tibia (17.4%).[5]

The spine is affected in 10–30% of cases, with tumors frequently involving the posterior elements, especially the lamina.[6-8] However, the lesion can involve all aspects of the vertebrae, including the vertebral body.[6] Accounting for 15% of spinal bone tumors, the lumbar spine is the most frequent vertebral location, whereas the thoracic and cervical spine (Figure 1) share equal frequency.[6-8]

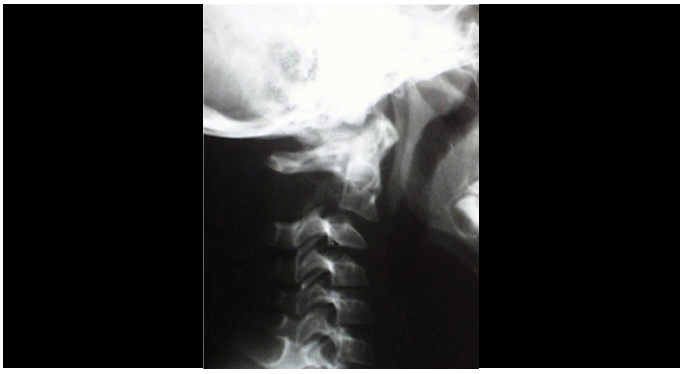

Figure 1. The plain film of the cervical spine (lateral view) showing a lytic lesion in the C2 vertebra, consistent with an aneurysmal bone cyst.

Etiopathogenesis

The etiology and pathogenesis of aneurysmal bone cysts (ABCs) remain not fully understood.[9] Initially, ABC was believed to result from a local hemodynamic disturbance, leading to increased venous pressure and the formation of a dilated vascular bed within the affected bone.[10] However, further studies have characterized primary ABC – previously considered a pseudotumoral lesion – as a true benign neoplasm.[11,12] The identification of a chromosomal translocation involving the upregulation of the ubiquitin-specific protease 6 (USP6) gene has defined at least a subset of ABCs as primary neoplasms.[13] The translocation of the ubiquitin-specific protease 6 (*USP6*) *Tre2* gene leads to transcriptional upregulation that activates nuclear factor kappa B (NF-κB) to induce matrix metalloproteinase production and initiate cyst formation.[13]

Currently, the clonal theory is the most widely accepted. Since Panoutsakopoulos *et al*.[11] and Oliveira *et al.*[12] demonstrated that a recurrent chromosome aberration t (16;17) (q22;p13) leads to a fusion gene of the entire ubiquitin-specific protease 6 (USP6 *alias* TRE2) coding sequence at 17p13 and the promoter region of the osteoblast cadherin 11 gene (CDH11) at 16q22, ABCs are more accurately considered a primary neoplasm.[9]

The translocation of USP6 and the promoter region of cadherin 11 leads to an upregulated expression of the otherwise structurally and functionally intact USP6,[14] which is part of the deubiquitinase enzyme family that removes ubiquitin from protein substrates, playing an important role for several regulation processes such as angiogenesis and inflammatory response.[14] USP6 rearrangements have been identified in 69% of primary ABCs and in none of the secondary ABCs by Oliveira *et al*.[12] The authors demonstrated that the effect of USP6 in the fibrous stromal component of ABCs leads to the expression of matrix metalloproteinase through activation of nuclear factor jB (NFjB).[15]

Diagnosis

Patients are usually symptomatic with local pain representing the most common symptom.[16,17] Progressive bone erosion may result in spinal instability, deformity and pathological fractures with neurological impairments which may suddenly exacerbate symptoms.[18] When located in the spine, ABCs also may cause neurological deficits due to mass effect, resulting in spinal cord and nerve roots compression.[7]

Following symptom onset, conventional radiographs generally provide the first diagnostic clues. Characteristic findings include an eccentric, metaphyseal, osteolytic lesion with internal septations and a "soap bubble" appearance, often associated with cortical thinning and expansion, with or without periosteal reaction.[19] The internal trabeculations confer a multilocular aspect.[20]

CT and MRI characteristics correspond to the underlying pathology, showing fluid–fluid levels circumscribed by blown-out thin layers of cortical bone (Figure 2).[3] CT helps delineate osseous margins and detect fluid density within the lesion.[19] MRI provides the most accurate image assessment for spinal ABC. In a study evaluating the accuracy of plain radiographs and MRI in diagnosing ABC, Mahnken *et al.* found that combining both modalities improved diagnostic sensitivity and specificity compared to either alone.[20] MRI typically shows multiple fluid-fluid levels within loculated cavities, reflecting blood sedimentation due to stasis. MRI may also reveal internal septations, perilesional extension, surrounding edema and demonstrate anatomical relationship between the lesion and the spinal cord and nerve roots.[21]

Diagnosis requires preferably a percutaneous bone biopsy to confirm ABC and rule out neoplastic processes such as chondroblastoma, giant cell tumor, or osteosarcoma, which share radiographic and histological similarities.[22] Macroscopically, ABCs appear as hemorrhagic, spongy masses covered by a thin layer of reactive bone. Histological analysis is essential for accurate diagnosis. Microscopically, they are characterized by abundant red blood cells and light brown hemosiderin filling cyst-like spaces separated by septa composed of fibroblastic proliferations, mitotically active spindle cells, osteoid, calcifications, and scattered multinucleated giant cells, as seen in Figure 3.[23]

Treatment

ABC causes significant morbidity, particularly in the spine.[24,25] Although the risk of malignant transformation is extremely low, treatment is necessary to prevent progressive bone destruction, pain,

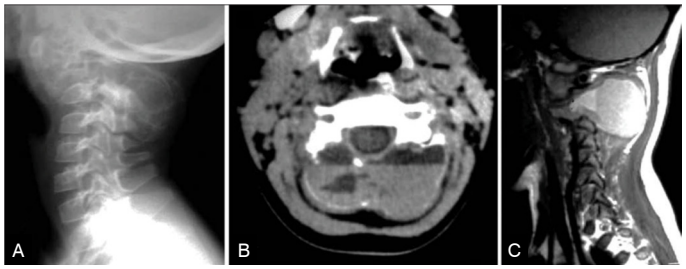

Figure 2. (Case 1) (A) The plain film of the cervical spine shows the "bubble" aspect of an ABC involving the vertebral body and the posterior arch of C2. Notice that the outer cortex is barely seen due the eggshell thin characteristic. (B) CT image at the level of C2 shows an expansible lytic lesion of the posterior arch with fluid-fluid levels. (C) The sagittal T1-weighted MRI shows the hyperintense fluid-fluid level inside the expanded cavity.

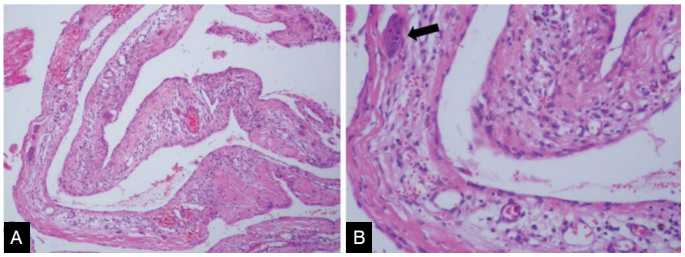

Figure 3. Histological appearance of the aneurysmal bone cyst. (A) Low-power microscopy view (hematoxylin and eosin; 4x magnification). (B) Higher-power microscopy showing a multinucleated giant cell (arrow) surrounded by fibroblasts within the septa (hematoxylin and eosin; 20x magnification).

and functional impairment. The primary therapeutic objective is the complete eradication of the lesion while minimizing the recurrence risk, preserving maximal bone integrity, and optimizing functional outcomes and pain control.

In this scenario, the optimal treatment of spinal ABC remains controversial.[5] Different therapeutic strategies have been described, ranging from pharmacological to surgical methods considering the morbidity and efficacy of each option, which may be implemented as alternatives or adjuvants to surgical resection.[3]

Because of their unique anatomical structure and function, there are special considerations when managing ABCs of the spine. The age of the patient, the surgical accessibility of the lesion, the necessity to minimize intraoperative blood loss, the presence of neurological compression, the presence of a pathological fracture and deformity, and potential postoperative instability after complete resection must be carefully considered.[6]

Curettage followed by bone grafting and resection has been the traditional treatment approach. Although surgical treatment remains a fundamental component of contemporary management, advances in the understanding of aneurysmal bone cysts (ABCs) and the consistently high recurrence rates reported in clinical series have driven the pursuit of alternative and less invasive therapeutic approaches.[17,19] The most frequent techniques described for spinal ABC include intralesional curettage, wide resection, selective arterial embolization, radiotherapy, and intralesional injection of bone-inducing agents.[26]

Surgery

Intralesional curettage with or without bone grafting has been described.[6] However, wide resection is the surgical treatment of choice for ABCs of the spine, especially in patients who present with a neurological deficit (ABAR). Early surgical intervention with total excision of all affected bone is recommended for immediate decompression.[27] Although *en bloc* resection is technically challenging,[28] this technique minimizes the risk of recurrence. Several reports also advocate *en bloc* resection of the spine.[6,28-31] Total excision, *en bloc,* if possible, provides the highest rate of cure, with an excellent prognosis.[6] Because the posterior elements are almost always involved, a posterior approach should be considered initially. With a posterior exposure, any tumor involvement of the pedicles with extension into the anterolateral aspect of the vertebral body (VB) is surgically accessible with a unilateral or bilateral transpedicular approach. If there is extensive anterior VB involvement and resection and decompression from a posterior approach are inadequate, then a separate anterior approach should be used, either in the same surgical procedure or later.[32]

Minimally Invasive Alternatives

Traditional surgical methods for the treatment of spinal ABC are associated with high recurrence rates, significant morbidity, and prolonged recovery periods.[5] These procedures entail significant risks, including intraoperative hemorrhage and injury to adjacent neurovascular and structural elements essential for maintaining segmental function.[15] Additionally, the anatomical complexity of certain lesion sites renders surgical access particularly challenging and potentially hazardous. Consequently, less invasive modalities have been increasingly advocated as first-line therapeutic options, especially for ABCs located in surgically demanding regions such as the spine and pelvis.[15] There is a growing emphasis on percutaneous treatment strategies aimed at minimizing surgical morbidity, particularly in the axial skeleton.[3,6-8,18,26-31] This paradigm shift is further supported by advances in the understanding of ABC pathophysiology and the observed responsiveness of select lesions to non-operative management, reinforcing the rationale for the development and adoption of minimally invasive techniques.

ABCs may be highly vascular, and when located in areas such as the spine or pelvis, surgical treatment becomes technically challenging and carries a high risk of hemorrhage and damage to vital structures.[32] In anatomically less accessible locations such as the spine, sacrum, and pelvis, several studies have demonstrated that minimally invasive techniques are a viable option to avoid significant surgical morbidity and mortality.[24,33]

Selective arterial embolization (SAE) is applied in the spinal and sacral tumor surgery to improve the therapeutic effects. The use of SAE to facilitate ABC resection by reducing intraoperative blood loss is well documented.[8,33] The intraoperative massive blood loss during resection of spinal and sacral tumors is a great challenge.[4] The effective control of intraoperative blood loss provides a significant assurance for the complete excision of spinal primary ABC. Embolization of feeding vessels is not only a preoperative procedure performed to reduce intraoperative bleeding, but also a primary therapy for spinal and sacral tumors. Henrichs et al. reported that selective arterial embolization of sacral ABCs could serve as an effective and safe treatment option.[34] The most important point to be taken into consideration is the influence of preoperative SAE on the blood supply to the wound.[33,34] Selective arterial embolization was originally employed as an adjuvant to surgical intervention, aiming to reduce intraoperative blood loss in highly vascularized ABCs. With advances in endovascular techniques and the challenges posed by surgical treatment, embolization has evolved into a definitive treatment option for ABCs in surgically inaccessible locations.[33] Selective arterial embolization using N-butyl-2-cyanoacrylate has been employed as a definitive treatment primarily for spinal lesions. However, this technique is not feasible in all cases, and its efficacy depends on the identification of a specific arterial feeder supplying the lesion. Moreover, caution is required when treating vertebral ABCs, given the need for precise visualization of critical arteries that, if inadvertently embolized, may lead to significant morbidity or even death. These include the artery of Adamkiewicz and the vertebral arteries, which must be excluded from the embolization field; otherwise, the procedure is contraindicated.[33] In the cervical spine, the technique carries a high risk of embolization involving the vertebrobasilar system, potentially resulting in ischemia of vital structures.[35] The risk of unintentional embolization of arteries supplying the spinal cord and brainstem further contraindicates its use in this region.[33] Adverse effects such as localized thrombosis at the puncture site, pulmonary embolism, osteocutaneous fistula formation, and extensive necrosis of surrounding tissues make this technique unsuitable as a first-line therapy in the absence of clear contraindications to other methods.[25] Additionally, the potential for severe complications supports the preference for alternative methods with lower associated risks.

The treatment of spinal ABCs presents unique challenges due to their location and proximity to critical neurological structures. Traditional surgical approaches, while effective, can be associated with significant morbidity, including potential neurological deficits, spinal instability, and prolonged recovery periods. These factors underscore the need for less invasive, yet equally effective treatment modalities. Commonly accepted non-surgical treatments such as embolization and injection of autologous stem cells or sclerosing agents have been the mainstay for treating spinal ABCs.[7,36,37] In 2017, Terzi et al. reported an algorithm for treating spinal localization of ABCs, which is still used today; however, due to the

complex nature of spinal lesions and the potential for recurrence, exploring targeted and innovative therapies becomes imperative.[38] Percutaneous techniques have been increasingly employed in the management of ABCs to reduce surgical morbidity. Among these, intralesional injection of calcitonin and methylprednisolone has emerged as a promising method. It was initially developed for the treatment of cervical spine lesions in pediatric patients, which carry high risks of severe complications due to inadvertent embolization of the vertebral artery and instability associated with surgical procedures.[39,40]

In this context, intralesional injection of calcitonin and methylprednisolone has emerged as a promising alternative to surgery, as suggested by case reports and case series.[16,17] Encouraged by favorable initial outcomes in these complex anatomical sites, we have expanded the use of this technique to include extra-axial locations in order to avoid surgical morbidity, with similarly positive results. However, due to the low prevalence of this neoplasm, studies involving larger patient cohorts remain scarce. Therefore, further research with a robust sample size is needed to establish the efficacy and safety of this therapeutic approach. Calcitonin downregulates the RANKL–RANK signaling pathway that governs osteoclast differentiation and activity. By inhibiting RANKL and promoting osteoprotegerin (OPG) expression in osteoblasts, calcitonin suppresses osteoclastogenesis and resorptive activity.[41] The available evidence strongly points to the RANK/RANKL signaling pathway between stromal cells and multinucleated giant cells as essential to the tumor's progression, making it a key therapeutic target. Calcitonin inhibits osteoclastic activity and promotes osteoblastic function, aligning with the histological and molecular findings observed in ABCs. It binds to calcitonin receptors on osteoclasts and osteoblasts, directly suppressing bone resorption while promoting calcium excretion and bone formation. Its effects on osteoclastogenesis involve blocking the RANKL-RANK interaction and enhancing OPG expression. In vitro studies confirm that calcitonin reduces the formation and activity. Pelle *et al*. have demonstrated the critical role of RANK/RANKL signaling in ABC pathogenesis using confocal microscopy. They showed that RANKL is strongly expressed by fibroblast-like stromal cells, while RANK is expressed by monocyte/macrophage precursors and multinucleated giant cells. Quantitative PCR revealed no significant difference in RANKL expression between ABC and GCT samples, both showing high levels of expression.[42] Yamagishi et al. also demonstrated increased RANKL mRNA expression in ABC, reinforcing the relevance of this pathway in its biology.[43] The limited apoptotic effect of calcitonin may explain its reduced efficacy when used alone. Thus, while it inhibits osteoclast formation and promotes osteoblast activity, this may not be sufficient to induce definitive trabecular bone formation and ABC ossification, as shown in Figure 4.

The synergistic effect with methylprednisolone, which inhibits fibroblast proliferation and has angiostatic properties, appears necessary to promote ossification and lesion resolution. Together, these actions support the hypothesis that calcitonin and methylprednisolone, through complementary effects on osteoclastic suppression, stromal cell inhibition, and angiostasis, can promote ossification and control of aneurysmal bone cysts. The clinical application of intralesional calcitonin and methylprednisolone is currently limited by the unavailability of injectable calcitonin in Brazil's healthcare system.

Similarly to calcitonin, by targeting the RANK/RANKL pathway, Denosumab offers a molecular approach to treatment that could potentially reduce tumor size (Figure 5), alleviate symptoms, and stabilize lesions without the immediate risks associated with invasive procedures.[7,22] Furthermore, in cases where surgery is eventually required, preoperative Denosumab treatment may facilitate less extensive and safer surgical interventions by reducing tumor vascularity and promoting ossification.[7,44] Denosumab, a RANK ligand inhibitor, is approved for the treatment of osteoporosis and prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.[8] Denosumab is a fully human monoclonal antibody that inhibits osteoclast maturation, activation, and function by binding to the receptor activator of the nuclear factor kappa-B ligand, with the final result being a reduced rate of bone resorption.[9] It has successfully managed GCTB and is approved for GCTB treatment.[10,11] Further, Denosumab has proven to be an off-label use sufficient in treating spinal ABCs, resulting in pain relief and neurological improvement in short-term follow-up, as demonstrated in Figure 6.[12,13] Whereas denosumab has been described as a definitive salvage treatment option for surgically unresectable lesions.[22] Denosumab, which blocks osteoclast-stimulated bone resorption, risks development of hypocalcemia and rebound hypercalcemia at the start and end of treatment, respectively.[42,45] Also, insufficient safety data on systemic use of Denosumab in children warrants further caution when considering it for pediatric ABC treatment because it has potential long-term side effects on the immature skeleton away from the ABC.[45,46] Denosumab is known to affect the physes of a child's growing skeleton in addition to the ABC, even after relatively short exposures, resulting in dense

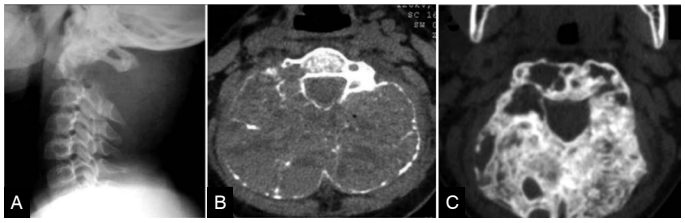

Figure 4. (Case 2) Plain film (A) of the cervical spine shows a soft-tissue mass at the topography of the C2 posterior arch, which is not seen. The CT scan (B) shows the egg-shell-thin cortex and the fluid-fluid levels. Notice the sparing of the cervical canal. The CT scan during the one year long follow-up (C) shows the progressive thickening of the outer cortex and concentric occupation of the cavities with bone until almost complete ossification of the lesion.

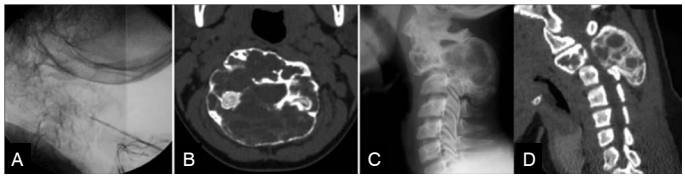

Figure 5. (Case 3) (A) Plain film of the cervical spine showing the needle inside the lesion that is involving the posterior arch of C2. (B) The CT scan demonstrates the expansive lytic lesion involving the body and posterior arch of C2, which presents fluid-fluid levels. The plain film (C) and sagittal CT scan (D) performed one year later show the shrinkage of the lesion and the ossification of its walls. Notice the reduction of size of the cavities.

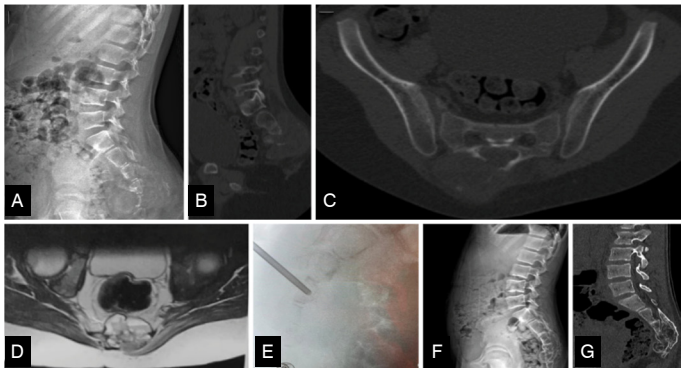

Figure 6. (Case 4) (A) Lateral radiograph of the lumbosacral spine showing the initial presentation of an aneurysmal bone cyst (ABC) in the sacrum. (B) and (C) display CT scans of the ABC, while (D) shows MRI. (E) shows the X-ray taken during intralesional injection of denosumab. (F) is a lateral radiograph of the lumbosacral spine taken 3 years after treatment, and (G) is a sagittal CT scan of the same region after the same follow-up period, both showing the ossified lesion.

metaphyseal bands on radiographs during treatment, and there are insufficient data to know what, if any, more permanent physeal injury could occur with longer medication exposure.[47] Last, recurrence risk of the ABC following cessation of Denosumab is also unknown.

Doxycycline has also been proposed as a sclerotherapy agent for spinal ABC treatment.[48,49] Doxycycline enhances bone formation by osteoblasts and inhibits MMPs, angiogenesis and osteoclast--mediated bone resorption.[48] Its effects should therefore counter some of those resulting from increased TRE17 production inherent in ABC pathophysiology.[48] Prior studies have demonstrated its success as a sclerotherapy agent treating primarily appendicular ABCs, with complication rates <5% and recurrence rates between 6% and 11%.[11] Most patients in those studies were clinically asymptomatic after doxycycline treatment. More recently, studies have assessed the success of doxycycline sclerotherapy as a treatment for spinal ABCs.[48,50] In a recent study Wong et al. concluded that image--guided doxycycline sclerotherapy is a safe and effective therapy for ABCs in difficult locations and should be considered a first-line standalone treatment option, after observing an 86% cure rate in the treatment of 14 cervical spine ABCs using image-guided doxycycline sclerotherapy.[49]

Alternative treatments such as radiation therapy have been reported. However, the authors do not recommend this method for the treatment of benign lesions due to the risk of myelopathy and its potential long-term adverse effects, including the development of secondary malignancies.[37]

All authors declare no potential conflict of interest related to this article.

CONTRIBUTIONS OF THE AUTHORS: Each author has made an individual and significant contribution to the development of this article. We define: MBRO: Project, Conceptualization, Methodology, Writing. PDCSS: References, Writing and Image Edition; AGCB: Supervision and Review; Luís LEC: Case selection and Review.

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