Clinical Case Report

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Combining of serial embolization and denosumab for large sacropelvic giant cell tumor

Case report of 3 cases

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Abstract

Rationale: Both serial arterial embolization (SAE) and denosumab have been proved to be effective in treatment for giant cell tumor (GCT). There is potential synergic effect of combining two methods. The purpose of current study is to justify a new treatment strategy of combination of SAE and denosumab as neoadjuvant or stand-alone treatment for large sacropelvic giant cell tumor.

Patient concerns: Pelvic and sacral GCTs tend to be very large size and vascular. The concerns of surgical treatment were invasiveness of extensive surgery, intraoperative hemorrhage, nerve function jeopardized and local recurrence. However, SAE alone may not be adequate for complete removal of the tumor.

Diagnoses: All the three cases were proved to be GCT by core-needle biopsy. Post-treatment pathological change was confirmed by further biopsy.

Interventions: The patient in Case 1 diagnosed of large recurrent sacral GCT received 6 times of endovascular embolizations with 2-month interval and started on denosumab simultaneously after first session of embolization. The second case was a 22-year-old female presented with a massive iliosacral tumor. SAE was performed for 3 sessions and the denosumab was started simultaneously. The patients was on treatment for half year. Both patients experienced a dramatic decrease in symptoms and concomitant improvement in function after the first embolization and weekly injection of denosumab. Tumor removal was performed on patient in case 2. The last case was a pelvic GCT and the patient received SAE and denosumab for half year. The tumor was then removed with purpose of complete cure.

Outcomes: The first patient was still on denosumab with stable tumor. The other two patients were both free of recurrence after surgical removal of the tumors. No denosumab was used postoperatively.

Lessons: We reported the first three cases treated by combination of SAE and denosumab in the literature and aim to raise an alternative method for large GCT at challenging anatomical locations, for which surgery would carry significant risk. SAE and denosumab can synergically promote sclerosis and result in significant decrease in pain. It is reasonable to consider using SAE combined with denosumab neoadjuvantly to reduce the extensiveness and morbidity of surgery, however further investigation is warranted.

Abbreviations: GCT = giant cell tumor, SAE = serial arterial embolization.

Keywords: denosumab, giant cell tumor, oncology, serial embolization, surgery

1. Introduction

Giant cell tumor (GCT) of bone is an intermediated, locally aggressive, primary bone tumor composed of mononucleated cells and evenly dispersed osteoclast-like multinucleated giant cells. It has been approved that the eponymous GCTs are not neoplastic; rather, their growth and proliferation is induced by the mononuclear stromal cells,[1] which is characterized by mutations in the histone H3 family 3A protein.[2] GCT usually arises in the appendicular skeleton with the most common site being the distal femur.[3] Within the axial skeleton, the pelvis and sacrum are most often involved, accounting for 1.5% to 8.2% of bone GCT.[4,5] Pelvic and sacral GCTs tend to be clinically silent in the early stages of development and cause few symptoms until they achieve a very large size and vascular. The challenges of management involved in late discovery, large size, difficulty in identifying local recurrence, high vascularity, nerve function preservation, spinal or pelvic instability, and potential of sarcomatous change.[6]

Typically, GCTs of pelvis and sacrum are treated with surgery, including curettage (with or without adjuvant) and excision, radiotherapy, and/or serial arterial embolization (SAE). SAE can be used neoadjuvantly for GCTs to facilitate surgical treatment,[7] since embolization has been shown to devascularize tumors, reduce size, induce calcification, and alleviate pain. The majority of patients with sacral GCTs demonstrate favorable response, and about 50% experience durable local control at 10 years follow-up.[8] SAE alone

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is a reasonable treatment option especially for the large recurrent GCTs located in pelvis and sacrum. Based on molecular biology of GCTs, systemic targeted therapy has been introduced, in addition to existing surgical treatment, with the aim of facilitating surgery at a later stage instead of performing more aggressive for complex cases.[6,9] Denosumab, a fully human monoclonal antibody that specifically inhibits receptor activator for nuclear factor-κ B ligand, has shown promise, particular for patients with tumors in challenging anatomical locations and those with recurrent disease.[10,11] The downstaging capacity of denosumab has been proved by several studies.[12,13] Histopathological findings of GCTs after denosumab treatment showed significant response with paucity or disappearance of giant cells and production of bone and fibrous tissue.[2,14]

In clinical practice, the treatment plan depends on feasibility of surgical resection and estimated risk for local recurrence. At the authors' institution, the treatment strategy for large unresectable or recurrent pelvic and sacral GCT evolved with denosumab utilized in clinical practice since 2014. Before year 2014, this group of patients were usually received SAE followed by surgical removal when operation became feasible. Due to the consistent finding of complete or near complete elimination of receptor activator for nuclear factor-κ B ligand-producing stromal cells and depletion of multinuclear giant cells, we started to accommodate denosumab in treatment for large pelvic and sacral GCTs since 2014. Given the uncertain clinical outcome of denosumab in this group of patients, SAE was kept being used. The rationale of combining strategy was based on the reported evidence: Denosumab can significantly reduce or eliminates bone destroying RANK-positive giant cell,[14] and SAE alone has been reported to achieve long-term local control,[8] which may be attributed to inhibit growth of mesenchysmal stromal cells. Two methods were responsible for 2 main cellular components of GCTs respectively, and there may be potential synergetic effect with introducing of both SAE and denosumab.

In order to explore the effectiveness and efficiency of combination treatment of SAE and denosumab, here we report our experience on 3 cases of managing large pelvic and sacral GCTs by combination of SAE and denosumab followed by surgical resection aiming at high chance of tumor control with acceptable morbidity. Written informed consent was obtained from the 3 patients for the current study.

2. Case reports

2.1. Case 1: sacral GCT

A 49-year-old male was referred to us for a 2-month history of dysuria and constipation. He received sacrectomy below S3 for GCT 2 years before. MRI and CT scan showed a large expansile sacral mass with cortical destruction; a biopsy was performed to rule out malignancy and local recurrence was confirmed (Fig. 1). Surgical removal carried extensive intraoperative hemorrhage and considerable morbidity. Treatment plan was discussed with the family, and the patient was scheduled for embolization from April 2014. Gelfoam (40–60 μm) or polyvinyl alcohol particles were used for high-selective occlusion, and coils were employed for prominent feeders. The embolization was performed every 1 to 2 months till December 2014 with 6 consecutive sessions totally for persistent vascularity. He started on denosumab after first time of embolization with induction dosing of 120 mg, once per week for 3 weeks, followed by 120 mg once per month. The patient went from being mildly symptomatic after the 1st month treatment to completely asymptomatic after 3 months treatment. Consecutive clinical and radiographic evaluation every 2 to 3 months after initial treatment revealed significantly tumor shrinkage and intralesional cystic change on MRI. The result was also evaluated by further biopsy performed after final embolization in December 2014. The pathological slides demonstrated significant response with paucity of giant cells and the production of fibro-osseous tissue. The SUVmax decreased from 7.09 at diagnosis to 2.49 after half year on treatment on regional PET-CT scan. The patient declined surgery and was still on denosumab at final follow-up of 31 months after initial treatment with stable disease and he was doing well.

2.2. Case 2: iliosacral GCT

A 22-year-old female presented with severe pain in her left buttock for 8 months, which severely restricted her gait. A large mass was palpated at left buttock. Radiograph revealed a massive pelvic tumor arising in the ilium (Fig. 2). A huge soft tissue mass had extended extraosseously. The histological diagnosis was GCT. SAE was performed for 4 sessions with 1-month interval, and denosumab was started simultaneously with 1st session of embolization. No further embolization was scheduled till tumor's vascularity disappears. After completion of the 3rd embolization, the buttock pain resolved significantly. CT scan showed significant reduction in tumor size, from $15.5 \times 14.1 \times 19.7$ cm at diagnosis to $10.1 \times 9.4 \times 8.2$ cm after 1 year on treatment, and impressive progressive sclerosis and ossification of the mass. MRI scan revealed extensive cystic change within the tumor. The SUVmax decreased from 12.1 to 3.6 on PET-CT scan. Also the patient reported pain relief and improvement in function. For the curative intent, surgical removal of the lesion was carried out at 1 year after diagnosis. Major portion of the tumor was en bloc resected and lesion located at iliosacral joint was resected by curettage with sacral nerve preservation. Spinoplvic stability was reconstructed by rod-screw system being augmented by bone cement (Fig. 3). Estimated intraoperative blood loss was about 1000 mL. No further denosumab was given after surgery. This patient made a successful recovery and was pain and disease free at 18-month follow-up.

2.3. Case 3: pelvic GCT

A 27-year-old female presented with left hip pain radiating down the lateral thigh and mass on left buttock. Initial imaging showed a large mass involving partial acetabulum, ischium, and pubis (Fig. 4). GCT was proved by biopsy. Given the high risk of local recurrence and potential extensive intraoperative hemorrhage by surgical resection alone, both SAE and denosumab were applied as the neoadjuvant role with the purpose of sclerotic rim formation. She then underwent 3 sessions of embolization and 7 doses of denosumab during the following 6 months. Subsequent CT scan at 6 months revealed sclerotic rim formed and the patient had a full relief of symptom. We opted surgical removal of the tumor after discussing with the patient and her families with the intent of complete cure at the current situation. The tumor was en bloc resected, involving acetabulum, ischium, and pubis, and a 3D-printed hemipelvic endoprosthesis was used to reconstruct the bone defect. The estimated blood loss during surgery was 1000 mL. The pathology specimen showed the soft-tissue mass developed an entire layer of bone. Histologic examination showed markedly cellular proliferation with mixed sheet-like

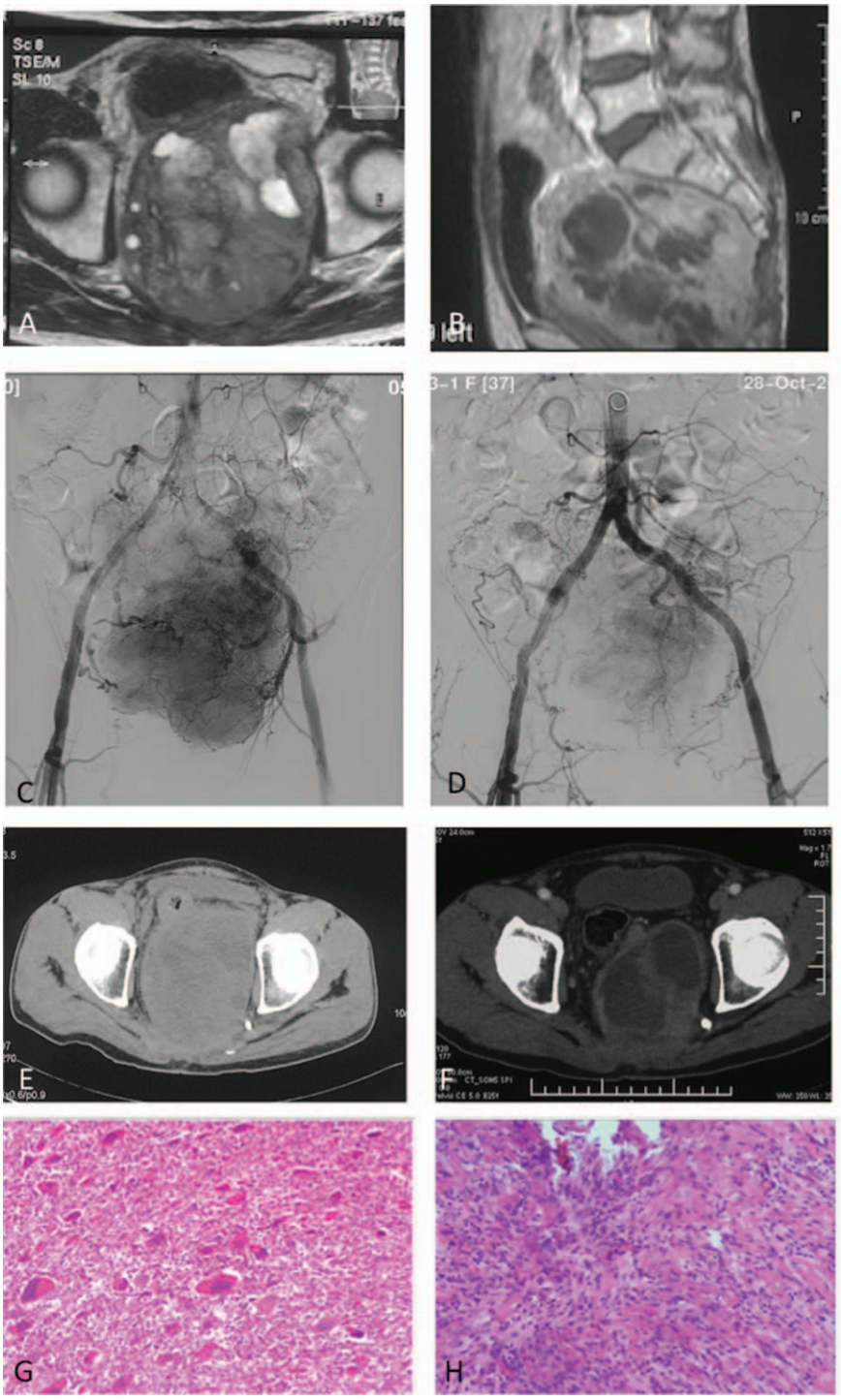

Figure 1. (A–H) The axial (A) and sagittal (B) MR images show a large expansile presacral mass after initial sacrectomy. Arteriogram images following 1st and 6th embolization demonstrate the vascularity pattern in the lesion. Markedly increased vascularity and uptake of contrast in the tumor is notable at initial presentation (C). Arteriogram following 6th embolization (D) demonstrates successful embolization. Same level axial CT scans at initial evaluation (E) and 8 months after treatment (F) reveal tumor shrinkage and intralesional cystic change within the tumor significantly. (G) The low power (Stain, hematoxylin & eosin; original magnification, ×10) before embolization and denosumab show typical appearance of giant cell tumor with 2 typical cell populations; mononuclear cells and multinucleated giant cells. (F) The biopsy performed after final embolization demonstrates significant response with a paucity of giant cells and the production of fibro-osseous tissue. CT = computed tomography, MR = magnetic resonance.

growth pattern, composed of mononuclear cells with vesicular and foamy histiocytes. The peripheral sclerotic rim was dominated by newly deposited bone and abundant fibrogen. At last follow-up, 8 months after surgery, the patient was doing well without evidence of local recurrence.

3. Discussion

To the best of our knowledge these 3 cases represent the 1st report of large sacral GCTs treated with combination of SAE and denosumab. Treatment for large GCTs in sacropelvis is very difficult and technical challenging. SAE alone was proved to be a

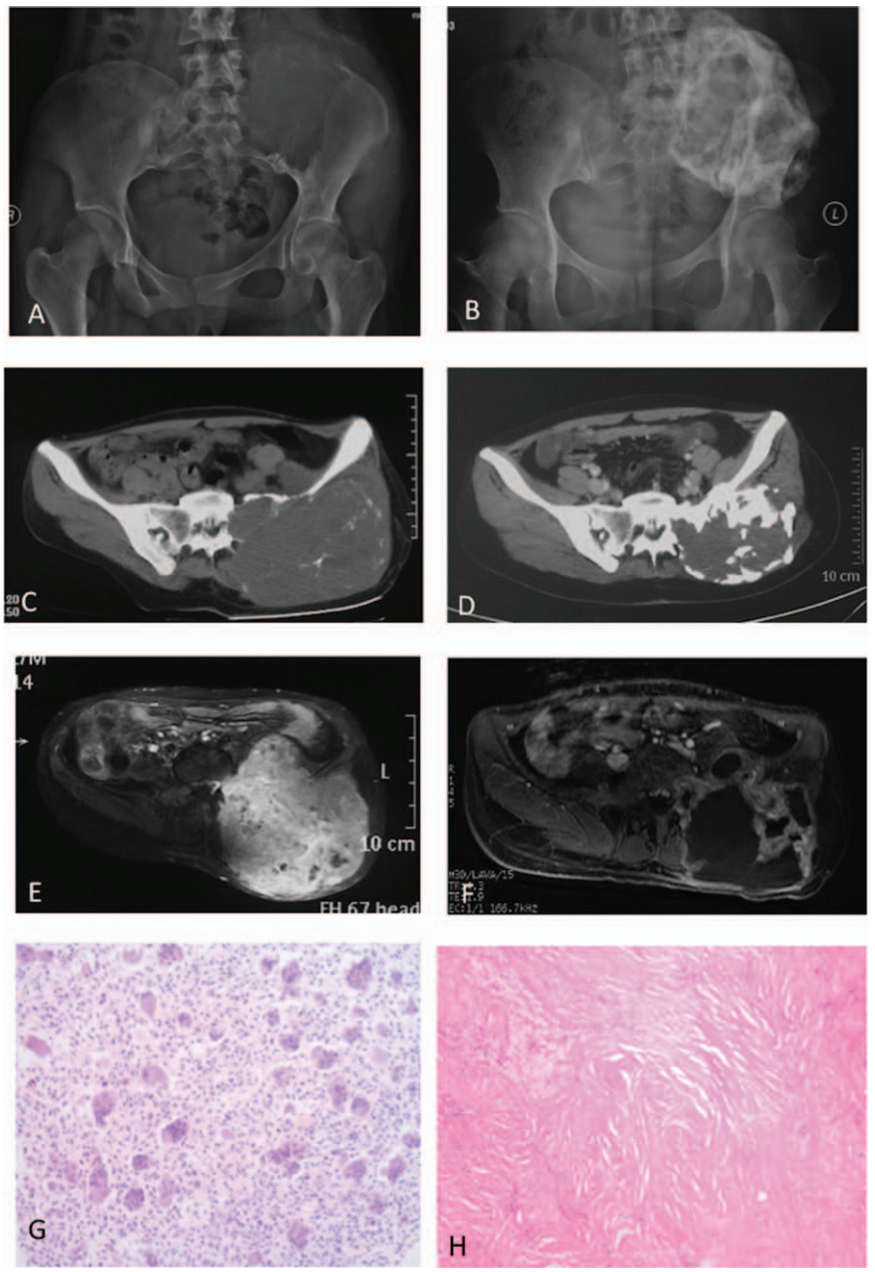

Figure 2. (A–H) A 22-year-old female with left pelvic large GCT. (A) Plain radiograph of the pelvis shows a large lytic lesion with involvement of left ilium and iliosacral joint. (C) Axial CT scan image demonstrates lytic lesion on left pelvis producing large soft tissue mass. (E) The fat-suppressed contrast-enhanced axial T1-weighted image shows significant enhancement. Parallel images obtained following SAEs and denosumab treatment demonstrated significant sclerosis both circumferentially and central part of plain radiograph (B) and axial CT scan (D). The contrast-enhanced image on the T1-weighted image reveals dramatically decreased enhancement. The postdenosumab treated samples are fibro-osseous lesion (H) compares with typical GCT before treatment (G). CT = computed tomography, GCT = giant cell tumor, SAE = serial arterial embolization.

curative treatment in sacral GCTs.[8,15,16] Denosumab has shown objective response of the tumor along with clinical benefit in patients with an inresectable tumor or large recurrences.[17] It is unclear whether combination of SAE and denosumab has synergetic effect and in which extent each treatment contributes to clinical response.

Lackman et al[18] reported 5 cases of sacral GCT treated with SAE alone and 4 tumors remained stable at a mean follow-up 6.7 years although no decrease of tumor size was observed. Lin et al[8] found response rate was 78% in a series of 18 sacral GCTs treated with SAEs. Also response to embolization was durable in about 50% of the patients at 10 and 20 years. Hosalkar et al[16] evaluated mid- to long-term outcomes of SAE as primary treatment modality and found no progression was achieved in 7 of the 9 cases at a mean follow-up of 8.96 years. No significant decrease in tumor size was observed. The most prominent change of SAE was pain relief, decrease in vascularity and peripheral ossification on radiographic imaging.[19,20] The reported typical interval of embolization was every 4 to 6 weeks.[15,19] Number of SAE was usually between 4 and 8 times.[8,16,18] The interval of embolization in the current 3 cases was 4 weeks, and number of embolizations was 6, 4, and 3, respectively, which showed a trend of decrease in the number of embolization, although similar effects of significant decrease in size and peripheral ossification

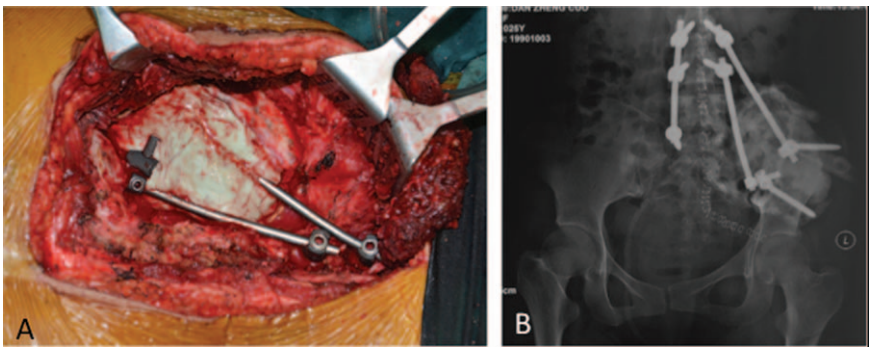

Figure 3. (A) Intraoperative photo shows the tumor was removed and the bony defect is filled with bone cement, and the lumbopelvic integrity is reconstructed with a spinal screw-rod system. (B) Postoperative plain radiography shows the reconstruction.

were observed in all the 3 cases. The 1st or 2nd time of embolization may be helpful to achieve rapid pain relief.

Denosumab has been proved to have downstaging capacity in an interim study of 222 patients, either a less morbid surgical procedure or no surgery.[12] The median duration of denosumab treatment for surgically treated patients was 14.2 months, while the patients had not received surgery and remained on denosumab for a median time of 19.5 months. A recent study showed denosumab provided favorable and consistent responses, which facilitated joint preservation surgery.[13] A minimum of 6

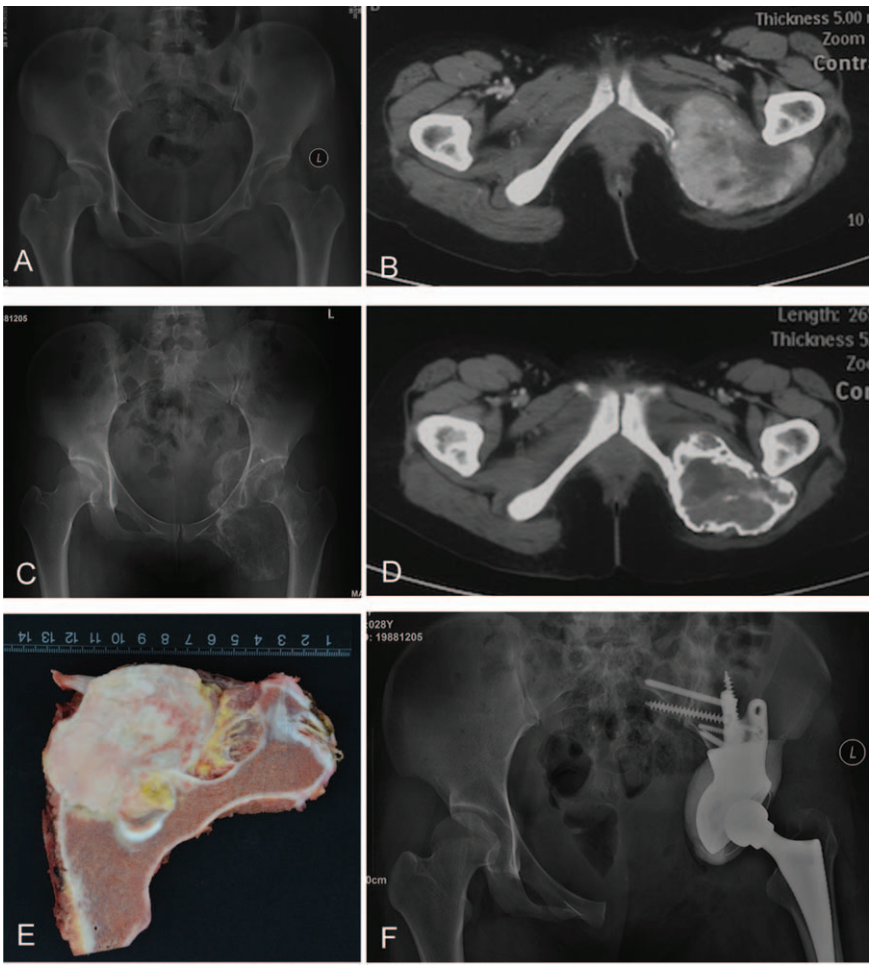

Figure 4. (A–F) A 27-year-old female with a left pelvic GCT. Initial plain radiograph (A) and axial contrast CT image (B) demonstrate the expansile, lytic lesion of a GCT involving partial acetabulum, ischium, and pubis with significant cortical destruction. Plain radiograph (C) and axial CT image (D) following treatment with SAE and denosumab demonstrate significant sclerotic rim formed. The tumor was en bloc resected, and gross image (E) of the hemipelvectomy specimen shows a peripheral edge of a sclerotic cortex and forms a solid mass with fibrous-like tissue. Plain radiograph (F) after surgery shows the bone defect was reconstructed with a 3D-printed hemipelvic endoprosthesis. CT = computed tomography, GCT = giant cell tumor, SAE = serial arterial embolization.

cycles of denosumab was planned before surgery, unless there was still evidence of ongoing clinical and radiographic improvement. For the 1st case, the response was prominent during the first 14 cycles on denosumab. The tumor was stable and progression free during the following 14 doses. Denosumab was used for 12 and 6 months in case 2 and 3, respectively. In case 2, decrease in tumor size was prominent during the first 8 cycles, and more ossification was the benefit for the following 4 months. The patient in case 3 reported free of pain after 6 cycles of denosumab and sclerotic rim was formed on CT scan. Given the plan of en bloc resection of tumor and less probability of further shrinkage of the tumor, the denosumab was stopped and surgical treatment was carried out. Earlier surgical intervention may achieve similar chance of local control, especially in the condition that en bolc resection was planned.[13] There are 2 reports[17,21] mentioned malignant transformation of GCTs while receiving denosumab treatment. Although it was impossible to confirm whether denosumab was causative or contribute to the development of the sarcoma, it is needed to be aware of the potential long-term effects following denosumab.

4. Conclusions

Combination of SAE and denosumab can be effective in treating large GCT at challenging anatomical locations, for which surgery would carry significant risk. SAE and denosumab can synergically promote sclerosis and result in significant pain relief. It is reasonable to consider using SAE combined with denosumab neoadjuvantly to potentially reduce the extensiveness and morbidity of surgery; however, further studies are necessary to evaluate the outcome following denosumab combined with SAE.

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