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Comprehensive treatment outcomes of giant cell tumor of the spine

A retrospective study

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Abstract

There is no consensus on a treatment strategy for spinal giant cell tumor of bone (GCTB) because of the difficulty in their treatment. Treatment options often include the use of the controversial denosumab, an antibody therapy aimed at tumor shrinkage, different curettage techniques, resection, or a combination of these therapies. The current study aimed to identify treatment methods associated with favorable outcomes in patients with spinal GCTB.

We retrospectively reviewed 5 patients with spinal GCTB, including patients with tumors of the sacrum, treated at our hospital between September 2011 and November 2020. Two men and 3 women were included in the study. The median follow-up period was 74 months (range: 14–108 months). We surveyed the tumor site, treatment method, denosumab use, and outcomes.

The median age was 17 years (range: 17–42 years). There were 2 cases of sacral GCTB and 1 case each of lumbar, cervical, and thoracic vertebral GCTB. The comorbidities observed included hepatitis, malignant lymphoma, atopic dermatitis, and asthma. The treatment method included zoledronic acid after embolization and denosumab, denosumab only, curettage and posterior fusion, and curettage resection after embolization and anterior and posterior fusion. Denosumab was used in all cases. Three patients were continuously disease-free, 1 patient with no evidence of disease, and 1 patient alive with disease.

Aggressive treatment, especially surgical treatment, may lead to good results in spinal GCTB.

Abbreviations: AWD = alive with disease, CDF = continuously disease-free, CT = computed tomography, GCTB = giant cell tumor of bone, MRI = magnetic resonance imaging, NED = no evidence of disease, PET = positron emission tomography, PET-CT = positron emission tomography-computed tomography, RANKL = receptor activator of nuclear factor kappa-B ligand.

Keywords: aggressive treatment, curettage resection, denosumab, giant cell tumor of bone, sacrum, spine, treatment

1. Introduction

Giant cell tumor of bone (GCTB) is an aggressive and rarely metastasizing neoplasm composed of neoplastic mononuclear stromal cells with a monotonous appearance mixed with macrophages and osteoclast-like giant cells.[1] GCTBs account for 4%–5% of primary bone tumors.[1] GCTB typically affects the end of long bones such as the distal femur, proximal tibia, distal radius, and proximal humerus in the mature skeleton and occasionally the metaphysis.[1] The most common location in the axial skeleton is the sacrum followed by the posterior elements of the spine.[2,3]

Spinal GCTB cases are challenging to treat because wide resections of the spine are technically difficult and tumor recurrence is common[3,4]; surgical treatment of spinal GCTB has been reported to have a recurrence rate of 22%–31%.[3,4] There is no effective chemotherapy for GCTB, and radiotherapy is reportedly contraindicated due to the side effects of spondylitis and the development of secondary malignancies.[5] Denosumab, a fully human monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the tumor necrosis factor family, has been approved for the treatment of adults with GCTB and skeletally mature adolescents with surgically unresectable GCTB.[6] The current retrospective study was conducted to provide evidence to determine treatment guidelines for spinal GCTB, including sacral tumors.

2. Patients and Methods

We retrospectively reviewed 5 patients with spinal GCTB, including that of the sacrum, treated at Kindai University Hospital. Two men and 3 women were included in the study (Table 1). The median follow-up period was 74 months (range: 14–108 months). We surveyed the tumor site, treatment method, denosumab use, and outcome. We obtained informed consent from all patients. The median age was 17 years (range: 17–42 years). The age of the

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The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Table 1

Patient characteristics.

Patients no.	Age	Sex	Site	Complain	Comorbidity	Treatment	Denosumab	Follow-up	Outcome
1	17	M	Cervical	Neck pain	Malignant lymphoma	Embolization, curettage, C1–C3 anterior and posterior fusion	12 times preoperative	74	CDF
2	17	M	1st lumbar	Low back pain	—	Curettage, T11–L3 posterior fusion	3 times, postoperative	80	CDF
3	16	F	12th thoracic	Back pain	Atopic dermatitis, asthma	T10–L2 posterior fusion	8 times, preoperative	17	CDF
4	42	F	Sacrum	Pain	—	—	5 times	14	AWD
5	34	F	Sacrum	Pain, neurogenic bladder	Hepatitis B	Embolization, zoledronic acid	21 times	108	NED

— = none, AWD = alive with disease, C = cervical spine, CDF = continuously disease-free, F = female, L = lumbar, M = male, NED = no evidence of disease, no. = number, Th = thoracic spine.

patients was bimodal, that is, between 16–17 years old and 34–42 years old. Two cases of GCTB involved the sacrum, 1 involved the lumbar vertebrae, 1 involved the cervical spine, and 1 involved the thoracic vertebrae. The comorbidities observed in this study included hepatitis, malignant lymphoma, atopic dermatitis, and asthma. GCTBs that were noninvasive to the surrounding tissue were considered to be indicated for surgery. In the case of invasive GCTBs, no indication for surgery was determined. The treatment methods included 1 case of zoledronic acid (10 times; 1 time/mo) after selective arterial embolization (using Gelfoam: Pfizer Co., New York, NY) once a month for 3 months and denosumab, 1 case of denosumab only, 2 cases of curettage and posterior fusion, and 1 case of curettage resection after a 1-time selective arterial embolization (using Gelfoam: Pfizer Co., New York, NY) and anterior and posterior fusion. Denosumab at a loading dose of 120 mg subcutaneous on days 1, 8, 15, and 29, and then again at 4 weeks was used in all cases. Two cases of GCTB of the sacrum were treated with denosumab once every 3 months after loading dose usage, one of which resulted in a marked response and the other resulted in an arrest of progression. None of the patients had side effects from denosumab. There were 3 cases of continuously disease-free survival, 1 case of no evidence of disease, and 1 case of alive with disease. The clinical outcomes of surgical and nonsurgical cases were also compared using chi-square test. A $P < .05$ was considered significant.

3. Case presentations and Results

We now present 3 cases treated using surgical intervention and 2 cases treated using nonsurgical intervention. The first 3 surgically treated cases are presented sequentially. The first patient was a 17-year-old boy (patient number 1 in Table 1) who presented to our hospital with a chief complaint of neck pain, which he first noticed upon waking up from sleep. A radiograph of the cervical vertebrae revealed erosion of the axis vertebra (Fig. 1A and B). Magnetic resonance imaging (MRI) revealed an isointense area on the T1-weighted image and a high-intensity area on the T2-weighted image (Fig. 1C and D). Positron emission tomography-computed tomography (CT) images also revealed bone erosion and accumulation on the lesion (maximum standardized uptake = 8.00) (Fig. 1E and F). We performed an open biopsy, and histology revealed a GCTB (Fig. 2A–C). We then performed curettage resection of the tumor and anterior and posterior fixation (Fig. 2B and C). Bone destruction was not significant; hence, embolization was performed first, and denosumab was administered 12 times. However, owing to persistent pain, curettage and C1–C3 anterior-posterior fixation were performed. The second surgically treated patient was a 17-year-old male (patient number 2). The patient visited our hospital with a chief complaint of lower back pain since 8 months. MRI revealed a tumor with extensive bone destruction in L1 (Fig. 3A and B); hence, a bone biopsy was performed. The pathological results

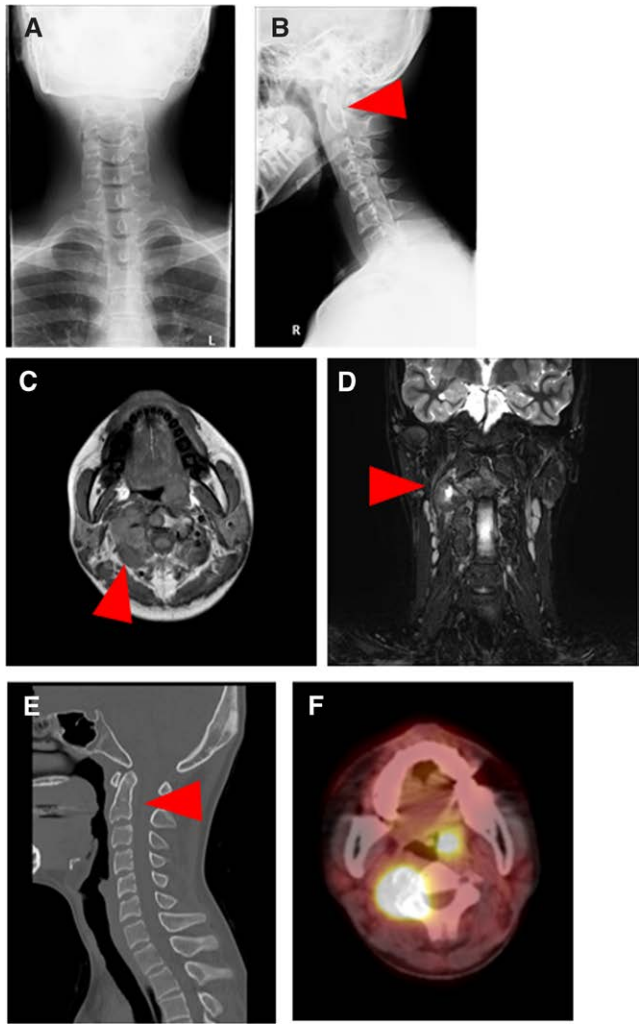

Figure 1. The representative images before the surgical treatment of Patient number 1 with the characteristics as described in Table 1. Coronal (A) and sagittal (B) radiographs of the cervical vertebrae. The radiograph of the cervical vertebrae showed erosion of the axis vertebra. Magnetic resonance image of the cervical vertebrae (C) and (D). The axial T1-weighted image shows the iso-intensity tumor mass in the axis vertebra (C). The coronal STIR image shows an iso-or high-intensity tumor mass in the axis vertebra (D). PET-CT shows an erosive lesion in the axis vertebra (E). Accumulation of SUV-max values = 8.00 (F). CT = computed tomography, PET = positron emission tomography, STIR = short TI inversion recovery, SUV-max = maximum standardized uptake.

of the biopsy resulted in a diagnosis of GCTB (Fig. 3C). Owing to the progressive bone destruction, surgery was considered.

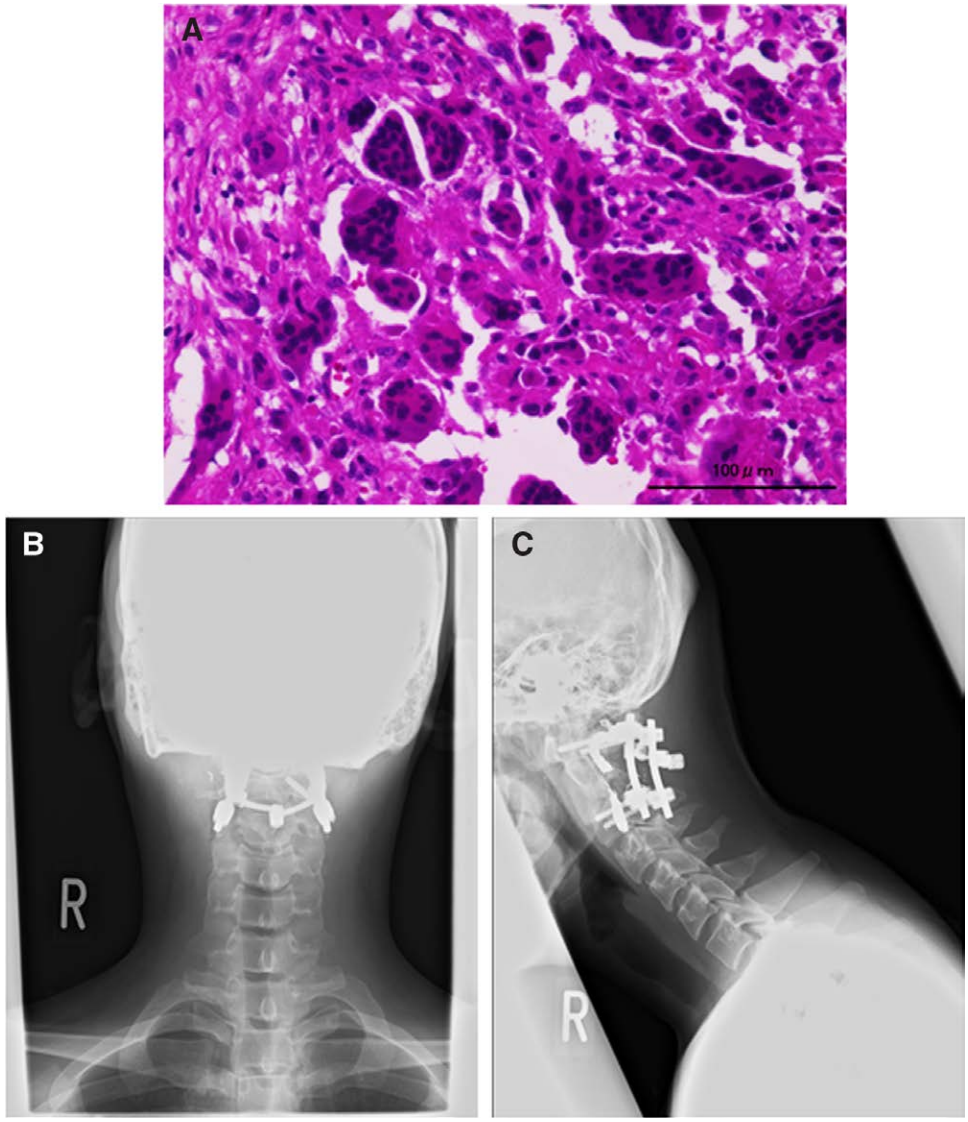

Figure 2. The representative images after the surgical treatment of patient number 1 with the characteristics as described in Table 1. The histological finding in hematoxylin and eosin staining shows some multiple giant cells (A). The proliferating round shape of mononuclear cells is also observed. No mitosis suggestive of malignancy is observed. Scale bar = 100 um. The radiographs are the coronal (B) and sagittal (C) views of the cervical vertebra.

Cage insertion into L1 and posterior fixation of T11–L3 were performed following curettage resection (Fig. 3D). Denosumab was administered a total of 3 times postoperatively as an adjuvant. Eighty months following the surgery, the pain resolved with no evidence of recurrence. The third patient who underwent surgical treatment was a 16-year-old female (patient number 3). The patient visited our hospital with a complaint of back pain since 6 months. CT (Fig. 4A and B) and MRI (Fig. 4C and D) revealed bone destruction at T12; hence, a biopsy was performed. The pathological findings resulted in the diagnosis of GCTB (Fig. 4E). The patient preferred to refrain from surgery as much as possible; therefore, treatment with 120 mg of denosumab once a month was initiated. Following a total of 8 denosumab treatments, the pain persisted; hence, a curettage and cage insertion into T12 and posterior fixation of T10–L2 were performed (Fig. 4F). At present, 17 months postoperatively, there has been no recurrence or pain. We now present the nonsurgical cases as follows. The first case (patient number 4 in Table 1), involving nonsurgical treatment, was that of a 42-year-old woman who presented to our hospital with a chief complaint of leg and lower back pain. CT revealed bone erosion of the sacrum (Fig. 5A) and MRI revealed a low-intensity area of the lesion on both T1- and T2-weighted imaging (Fig. 5B and C). Positron emission tomography-CT revealed accumulation of the lesion with an maximum standardized uptake value of 10.0 (Fig. 5D). We performed a needle biopsy under CT guidance.[7] Histology revealed multinucleated giant cells and the growth of mononuclear cells (Fig. 5E). We determined the lesion to be inoperable owing to the extent of its spread and involvement of a large area within the sacrum; thus, surgical treatment could result in the paralysis of the lower extremities and impair bladder-rectal function. Therefore, she was treated with 120 mg of denosumab once every 8 weeks for 1 year following a loading dose of 5 courses of 120 mg of denosumab intermittently.[8] After treatment, the CT images revealed hyperplasia of the calcaneus surrounding the tumor (Fig. 5F). The second patient treated nonsurgically was a 34-year-old female (patient number 5) who presented to the clinic with a chief complaint of pain in the buttocks for the past 5 months. CT (Fig. 6A) and MRI (Fig. 6B and C) revealed bony destruction of the sacrum; hence, a biopsy was performed. Following the biopsy, a diagnosis of GCTB was made (Fig. 6D). We determined that surgical treatment to be impossible owing to involvement of a large area within the sacrum; thus, surgical treatment could result in the paralysis of the lower extremities

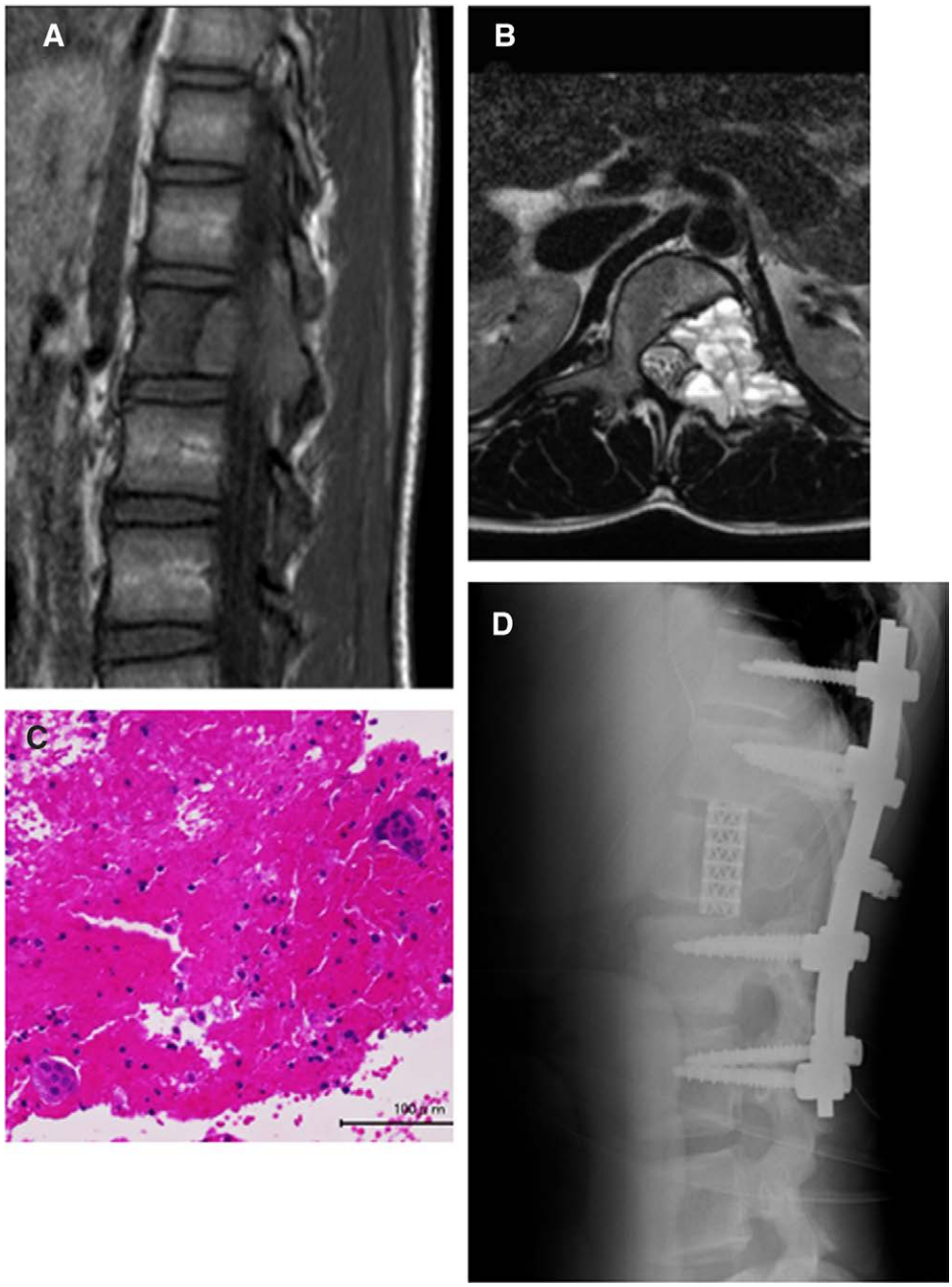

Figure 3. The representative images of patient number 2 with the characteristics as described in Table 1. The sagittal T1-weighted MRI of the vertebra (A). The low-iso intensity tumor mass is observed spreading inside and outside the vertebrae (B). The axial T2-weighted MRI of the vertebra. The high-intensity tumor mass is observed spreading inside and outside the vertebrae (B). The pathological findings as indicated by hematoxylin and eosin staining (C). A few multinucleated giant cells are observed (C). The sagittal (D) radiograph of the vertebra after surgical treatment. A cage inserted in L1 and fusion from T11 to L3 is observed. Scale bar = 100 μm. MRI = magnetic resonance imaging.

and impair bladder-rectal function. Therefore, selective arterial embolization was performed for 3 months. The pain did not resolve, and monthly injections of zoledronic acid were added to the treatment regimen. Zoledronic acid was administered 2 weeks following each arterial embolization. Following 10 months of treatment with zoledronic acid, the patient's symptoms still did not improve; therefore, the treatment protocol was revised to denosumab 120 mg once a month. By the third dose, the pain in the buttocks had decreased. At 10 months, CT revealed bone sclerosis appearing around the sacrum (Fig. 6E). In comparing surgical and nonsurgical cases by chi-square test, significantly more surgical cases were continuously disease-free (no recurrence) ($P = .025$).

4. Discussion

The clinical evidence of spinal GCTB is limited and the treatment methods are controversial.[3] We retrospectively reviewed 5 spinal GCTB cases treated at Kindai University Hospital between September 2011 and November 2020 to determine a more cohesive treatment strategy for patients with spinal GCTB.

Previous studies have shown that the mean age of spinal GCTB occurrence is approximately 30 years.[9,10] The peak incidence is in patients aged between 20 and 45 years, with approximately 10% of cases occurring in patients in their 20s.[11] The biological behavior of the disease in younger patients is similar to that seen in adults, except for a marked female preponderance, the principles of treatment, recurrence patterns, and course

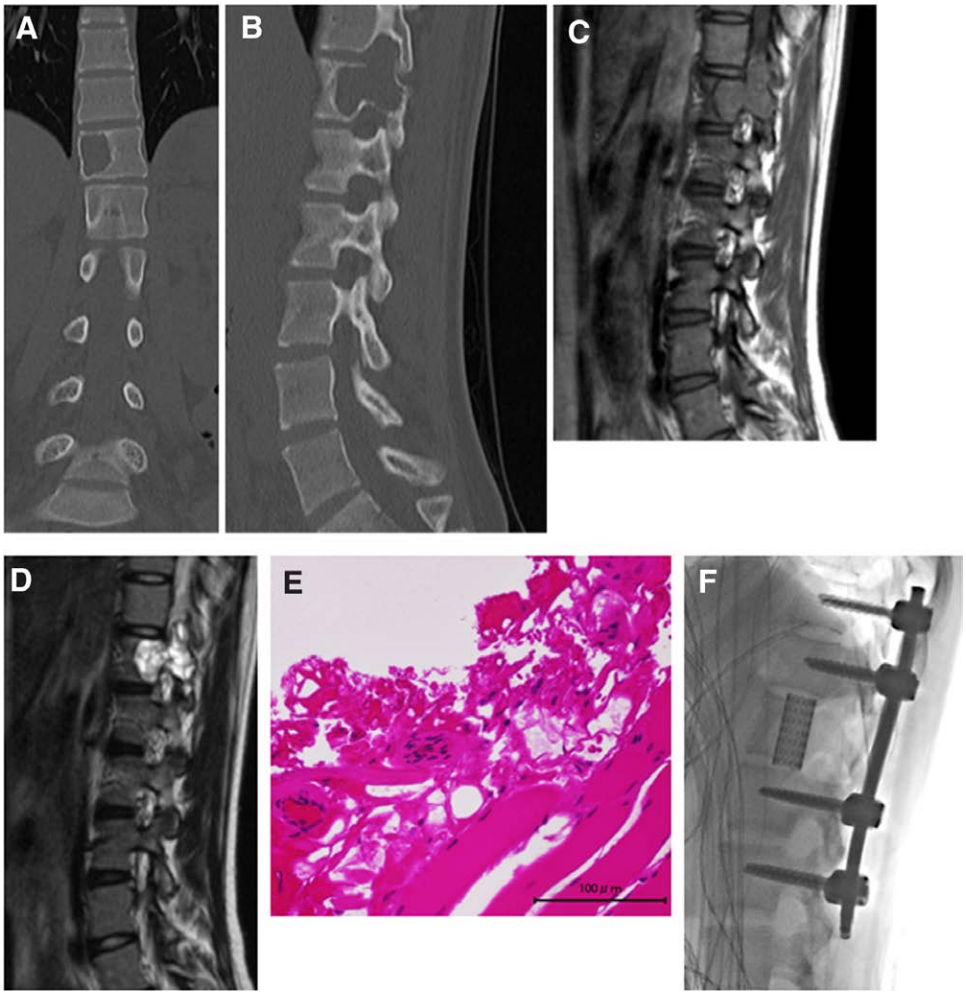

Figure 4. The representative images of patient number 3 with the characteristics as described in Table 1. The coronal (A) and sagittal (B) CT image of the vertebra. A few multinucleated giant cells are observed. The sagittal T1-weighted MRI of the vertebra (C). The tumor mass as indicated by the low-intensity area spreading out is observed in T12. The T2-weighted MRI of the vertebra (D). An osteolytic lesion is observed in T12. The pathological findings as indicated by hematoxylin and eosin staining (E). The tumor mass spreading out is observed in T12. The sagittal radiograph of the vertebra following surgical treatment (F). A cage inserted in T12 and fusion from T10 to L2 is observed. Scale bar = 100 μm. CT = computed tomography, MRI = magnetic resonance imaging.

of the disease mirroring the behavior of its adult counterpart as previously described.[12] Although treatment of GCTB in young adults has been reported to be similar to that in adults, it is important to note that children younger than 12 years of age are not candidates for denosumab because they have immature skeletons.[12,13] In the current study, preponderance was not observed and sacral occurrence was limited to patients in their 30s to 40s. Moreover, a bimodal age of occurrence was observed between the 16–17 and 30–40 age groups. The patients treated surgically were all in their teens, while those treated conservatively were all in their 30s and 40s, thereby showing a bimodal pattern. All patients included in the study were within the indicated age range for denosumab administration, and treatment decisions were made based on individual patient conditions.

Severe local pain was reported by the patients in this study, as previously described.[14] A previous study also showed that pain was the most common complaint and was observed in 74.6% of patients.[10] Moreover, other studies have shown that neurological pain is also a salient feature of GCTB.[15] All patients in the present study experienced local pain, and 1 patient demonstrated a neurogenic bladder. Local pain is one of the most prominent complaints in patients with spinal GCTB, needing swift and effective pain management, regardless of age. Moreover, symptomatic treatment was required for neurogenic pain of sacral origin, which was not considered an indication for surgery in the present study.

The standard treatment for aggressive GCTB is surgery (curettage or wide resection), which can offer pain relief and better prognoses in some patients who are eligible for surgery (resection). Surgical procedures applicable to the spinal column include curettage resection, piecemeal total spondylectomy, and total en bloc spondylectomy.[10,16]A previous study suggested that total en bloc spondylectomy could significantly decrease the recurrence rate of aggressive spinal GCTB.[10] Curettage resection can be used for small lesions limited to the anterior cervical column, and anterior stabilization can be used for lesions limited to the vertebral corpus in cervical spine GCTBs.[17,18] Surgery in these cases is performed in 2 stages, anterior and posterior, for cases undergoing large excision. Anterior and posterior fusion are used to prevent instability after excision.[18,19] In the current study, we performed curettage resection in patients who underwent surgical treatment. In addition, we performed posterior fusion in 2 patients and anterior and posterior fusion in 1 patient. In the cases presented in this report, tumor resection was accompanied by fusion. Regardless of age, if the patient agrees and the site is suitable for surgery, aggressive surgical treatment should be considered.

There have been reports of good results with surgical treatment after embolization alone.[14] However, some studies reported favorable outcomes after treatment with a combination of surgical treatment and adjuvant drug therapy.[9,10,15,20] The typical drug prescribed is denosumab.[9,20,21]

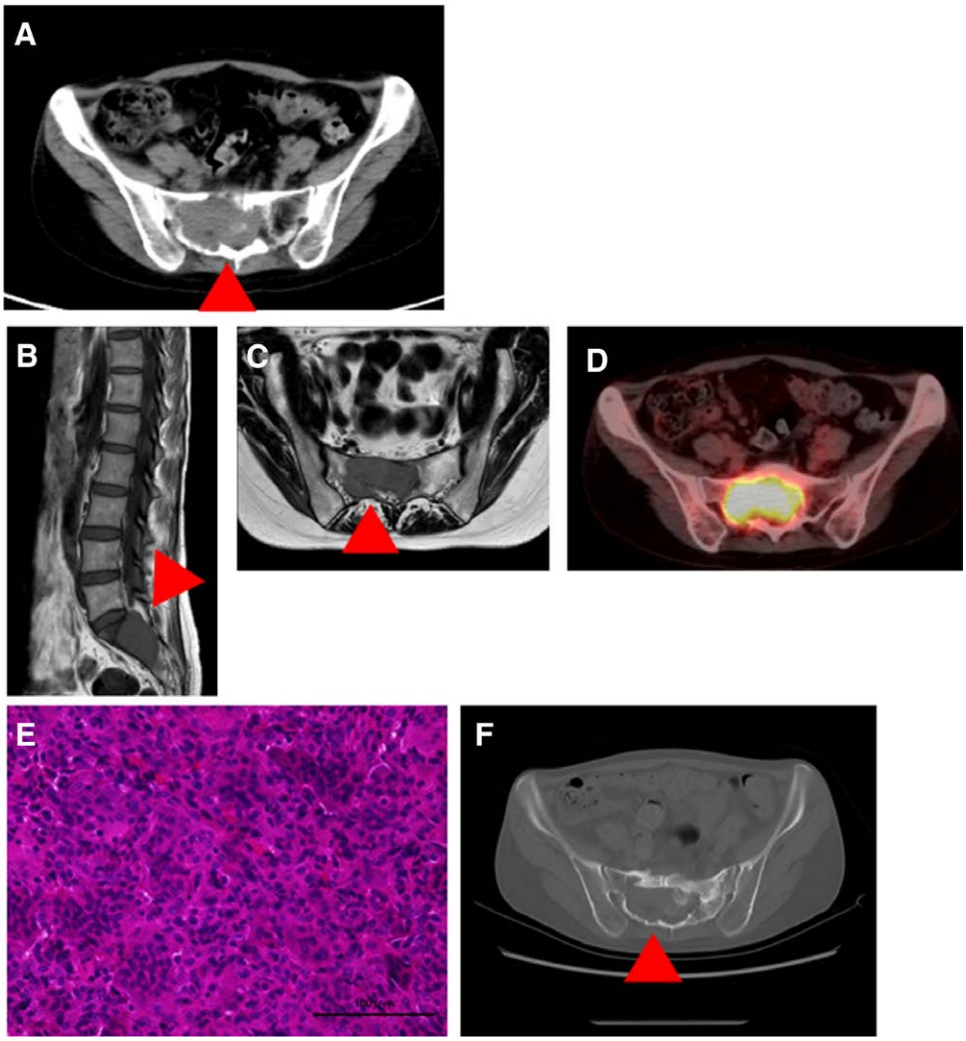

Figure 5. The representative images of patient number 4 with the characteristics as described in Table 1. The axial CT image of the pelvic bone at the initial visit (A). An erosive lesion is observed in the sacrum. T1-weighted (B) and T2-weighted (C) images at the initial visit show a low-intensity lesion (B and C) in the sacrum. PET-CT shows the accumulation of the bone lesion (D). Hematoxylin and eosin staining showed multiple giant cells (E). A proliferating round shape of mononuclear cells is also observed. No mitosis suggestive of malignancy is observed. Scale bar = 100 um. CT shows bone remodeling around the sacrum (F). CT = computed tomography, PET = positron emission tomography.

Denosumab, a RANKL inhibitor, has been approved by the US Food and Drug Administration for neoadjuvant drug therapy in advanced GCTB.[22] In general, 3–4 months of neoadjuvant denosumab (at a dose of 120 mg subcutaneous on days 1, 8, 15, and 29, and then again at 4 weeks) should be incorporated in the multidisciplinary treatment for all patients with advanced GCTB who are not candidates for primary curettage.[23] However, it should be noted that it is not indicated for use in patients younger than 12 years of age who have immature skeletons.[13]

The neoadjuvant use of denosumab is intended to facilitate surgery, technically facilitating local curettage and resection and resulting in local tumor control. However, an increasing number of studies have shown the adverse effects of denosumab treatment on GCTB.[23,24] Denosumab may increase the risk of local recurrence in patients with GCTB who have undergone curettage.[25] Tumor cells are trapped in the thickened neoplastic bone by denosumab, which inhibits adequate curettage.[26] It has also been reported that denosumab may cause malignant transformation of GCTB.[22]

No recurrence or malignant transformation was observed in the cases analyzed here. In general, preoperative denosumab treatment may be necessary because of the high-risk and highly invasive nature of cervical spine surgery. Therefore, postoperative treatment may not be necessary.

Surgical treatment of GCTB of the sacrum is challenging. However, denosumab is effective for GCTB of the sacrum, as previously described,[9,21] in some cases when combined with surgery.[9] Conservative treatment for GCTB of the sacrum including sacrum epidural injection and analgesics has also been reported to be useful.[9] The cases analyzed in this study demonstrated GCTB of the sacrum that was difficult to treat with a surgical approach; hence, we treated them with denosumab and embolization or caudal block injection. A decrease in the GCTB lesion was observed in 1 case, and alleviation of symptoms was observed in the other. When the surgical approach is difficult, conservative treatment with denosumab is considered an option. Although many clinical trials have been conducted using denosumab for the treatment of GCTB, much remains to be learned about the optimal duration of treatment. There is concern that discontinuation of denosumab may lead to a higher rate of subsequent local recurrence.[27] Chawla et al[22] recommended a lower dose or less frequent administration of denosumab for the maintenance of patients with unresectable GCTBs. The patients in this report continued to use denosumab at a reduced frequency. In summary, denosumab was

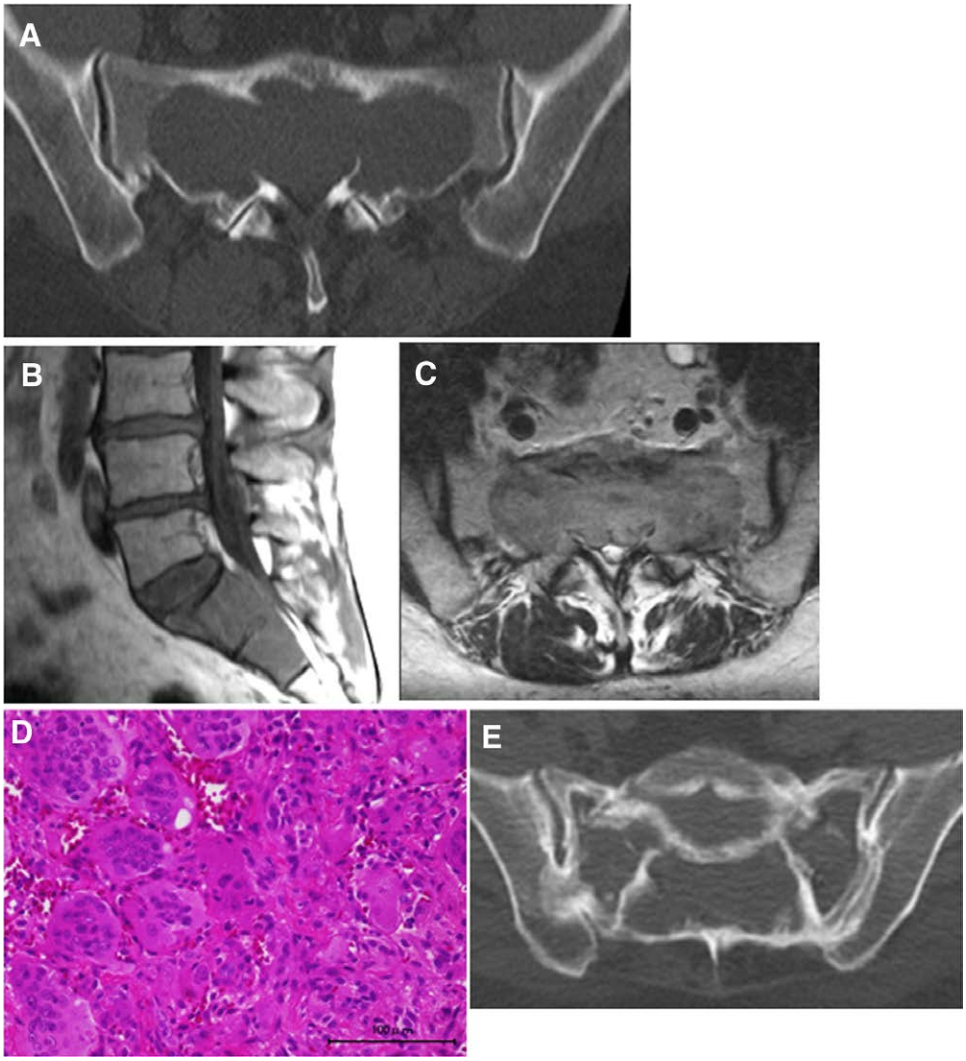

Figure 6. The representative images of patient number 5 with the characteristics as described in Table 1. The axial CT image of the sacrum (A). An osteolytic lesion is observed in the sacrum. The sagittal T1-weighted MRI of the sacrum (B) and axial T2-weighted MRI of the sacrum (C). The tumor as a low-iso intensity lesion is observed to have spread within the sacrum. The pathological findings as indicated by hematoxylin and eosin staining (D). A few multinucleated giant cells are observed. CT scans revealed bone sclerosis appearing around the sacrum at 10 months after commencing denosumab treatment (E). Scale bar = 100 μm. CT = computed tomography, MRI = magnetic resonance imaging.

used primarily as preoperative adjuvant therapy in the surgical intervention cases in the current study and as primary treatment of the underlying disease in the nonsurgical treatment cases.

After treatment with denosumab, although infrequent, changes in cell count and the presence of new bone in histopathological specimens may necessitate differentiation from malignancy.[28–30] Pathological changes after treatment with denosumab may reflect a shift in the balance between RANK-mediated bone resorption by osteoclasts and bone formation induced by stromal cells.[31] There were no cases with obvious changes pre- or post-surgery in the current study.

Between 15% and 50% of conventional GCTB recur locally after curettage and usually within 2 years.[1] Recurrence is observed in less than 20% of cases, and early detected cases are usually treated by re-curettage resection.[32] Lung metastasis occurs in 5% of cases.[33] In the current study, the cases treated with curettage resection and denosumab did not show recurrence or metastasis. Treatment with curettage and denosumab are likely to lead to favorable outcomes in GCTB of the spine. Moreover, conservative treatment, mainly denosumab, should be aggressively used in cases wherein surgical intervention is contraindicated. In addition, all teen patients were in remission in the current study, while all patients in their 30s and 40s were not, although they received different treatments. This is very interesting because there seems to be a correlation between age and treatment outcome. Future comparative studies on treatment results by age group are needed.

The current study had some limitations. First, the number of cases involved was small, which weakened the significance of the statistical analysis. Further large prospective comparative studies evaluating surgically and nonsurgically treated cases are warranted in the future. Second, the study was retrospective and the treatment strategy was inconsistent. In addition, the long-term safety, optimal maintenance dose, frequency for pregnant patients, and treatment strategies remain unclear. A comparison between patients using and not using denosumab is also unavailable. However, the strength of the study was that it was longitudinal, spanning 14–108 months, and provided detailed and thorough information on multiple patients. Large-scale prospective clinical trials are needed to resolve these issues.

5. Conclusions

Aggressive surgical treatment of GCTB of the spine, except in noninvasive cases, is necessary to obtain a favorable prognosis.

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Author contributions

Conceptualization, K.H., H.M., K.T., T.I., M.A., and S.N.; methodology, K.H., H.M., K.T., and S.N.; software, K.H., T.I., H.M., and S.N.; validation, K.H., S.N., H.M., and M.A.; formal analysis, K.H., K.T., T.I.; investigation, K.H., S.N., H.M., K.T., T.I., and M.A.; writing—original draft preparation, K.H.; writing—review and editing, K.H., H.M., K.T., T.I., M.A., and S.N.; All authors have read and agreed to the published version of the manuscript.

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