Vertebral Osteomyelitis with Profound Neurologic Deficit: Successful Treatment with rhBMP-2 and Titanium Cage Device

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ABSTRACT

The efficacy of bone morphogenetic proteins (BMP) in infection has not yet been established. Since fusion is a necessary aim in the treatment of vertebral osteomyelitis with spinal instability, BMP may be a helpful adjunct in the surgical treatment of these cases. We present a case of vertebral osteomyelitis associated with neurologic deficits, treated with decompression and fusion using recombinant human bone morphogenetic protein-2 (rhBMP-2) and titanium cage device. Eradication of infection, recovery of neurologic deficits, spinal stabilization and solid fusion were achieved and maintained at 5 years follow-up.

Key Words: bone morphogenetic proteins, rhBMP-2, titanium cage, vertebral osteomyelitis.

Introduction

The treatment of vertebral osteomyelitis is challenging. Diagnosis is often delayed for an average of two to three months. Medical management alone, in the form of systemic antibiotics and bed rest or external immobilization, has been shown to have a high failure rate, particularly in the presence of neurologic deficit and spinal instability.[1,2] Despite advances in surgical techniques and antibiotic coverage, mortality rates from pyogenic spinal infections remain as high as 20%, primarily because of concomitant illnesses and patient status.[3,4] Consequently, elderly patients have even higher morbidity and mortality rates.

In the face of pyogenic infections, there has been a general reluctance to use metallic implants. However, the morbidity of the associated external immobilization and/or prolonged recumbence is substantial. Furthermore, internal fixation maintains spinal stability and alignment, prevents postoperative kyphotic deformity and promotes bony fusion. Therefore, there has been a migration to rigid spinal stabilization. With the development of titanium instrumentation, this trend appears to be increasing, as this material has the advantage of being more resistant to bacterial surface colonization than stainless steel.[5] The use of titanium surgical mesh to reconstruct destroyed and infected vertebral bodies is gaining more traction.

Once the spine is stabilized with instrumentation, the surgeon must still achieve the biologic solution of fusion. In the past, the preference has been to use large volumes of autogenous cancellous bone graft. The availability of this bone graft, however, is somewhat limited in all patients. In older patients, it also appears that there is a significant decrease in the concentration of viable, pluripotential cells to form osteoblasts. This makes the source of bone graft material even more problematic in this patient population. Bone morphogenetic proteins, first described by Marshal Urist in 1965, are known to help pluripotential mesenchymal cells differentiate into osteoblasts which form bone.[6] Recombinant human bone morphogenetic protein-2 (rhBMP-2), a genetically engineered version of the protein, may provide a viable alternative for enhancing fusion in this setting. This is a case of an elderly patient in whom neurological deterioration mandated decompression, stabilization and fusion using rhBMP-2 and titanium mesh cage. We present the 5-year clinical and radiographic outcomes of this technique which is the longest follow-up described to date.

Case Report

Our patient is a 68-year-old nun at a local convent who, a month prior to her admission, began to experience vague pains over her upper back, along the interscapular area. There was no inciting trauma. After about a week, she started noticing urinary disturbance in the form of a sensation of incomplete voiding. After about another week, she started experiencing numbness and weakness of both lower extremities, such that she began having difficulty with standing and walking.

With these symptoms, she was then admitted to a local community hospital, where workup done included a chest computerized tomography (CT) scan, a bone scan, a magnetic resonance imaging (MRI) scan of the thoracic spine, and a CT-guided needle biopsy of a paravertebral abscess. This aspirate yielded growth of coagulase-negative *Staphylococcus aureus*, and she was promptly started on intravenous nafcillin. Other laboratory results included

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elevated values of erythrocyte sedimentation rate (ESR) at 38 mm/hr, C-reactive protein (CRP) at 20 mg/L, and white blood cell (WBC) count at 12,000 cells/mcL. After five days in the hospital and with further progression of her weakness, she was then transferred to our institution.

On admission, she was noted to be alert, oriented and not in distress. She was unable to stand and was only examined laying on her bed. Inspection of her back revealed no skin lesion, no gibbus, no marked deformity, but with tenderness to palpation over the upper thoracic area. There was dysesthesia over her left chest wall, corresponding to dermatome levels T3-T4. While she had full motor strength of both upper extremities, she had profound weakness of both lower extremities, with a grade of only 2/5 for all major muscle groups. Deep tendon reflexes were brisk bilaterally, with a positive Babinski sign but no clonus. Light touch sensation was present but mildly decreased over both lower extremities.

CT and MRI scans of her thoracic spine revealed lytic destruction of the T3 and T4 vertebral bodies with obliteration of the intervertebral disk space. A large paraspinal mass at this level, measuring approximately 2.5 x 5 cm, extended into the right pleural space. There was also extensive epidural soft tissue as well as retropulsed vertebral body fragments present, causing compression of the thoracic spinal cord. The imaging findings were consistent with the diagnosis of vertebral osteomyelitis (Figure 1).

Given the imaging findings and the presence of profound and progressive weakness not improving with intravenous antibiotics alone, it was deemed that emergent decompression was necessary to prevent further deterioration and permanent neurologic damage.

Corpectomy of T3 and T4 using the costotransversectomy approach was performed to decompress these levels. A thoracic surgeon assisted in debridement of the posterior mediastinal mass, which intraoperatively had an appearance consistent with an abscess. The vertebral bodies of T3 and T4 had been destroyed by disease.

After thorough decompression, a titanium mesh cage was packed with an absorbable collagen sponge soaked with rhBMP-2 (Infuse Bone Graft, Medtronic Sofamor Danek) and cancellous allograft bone (Figure 2). This took the place of the T3 and T4 bodies, and spanned the defect. One Large II kit of Infuse Bone Graft, a total of 12 mg of rhBMP-2, was utilized. Posterior segmental fixation from T1 to T6 was then obtained using a multiaxial titanium pedicle screw and rod system (CD Horizon Legacy, Medtronic Sofamor Danek). Removal of the remaining facets and decortication of the laminae were then performed, prior to placement of remaining allograft bone and rhBMP-2, in order to obtain posterior fusion.

At the time of discharge to the rehabilitation center one week after surgery, strength in her lower extremities had already improved to 3-4/5 for the quadriceps and gatrocnemius-soleus, but still only 2/5 for the tibialis anterior and extensor hallucis longus.

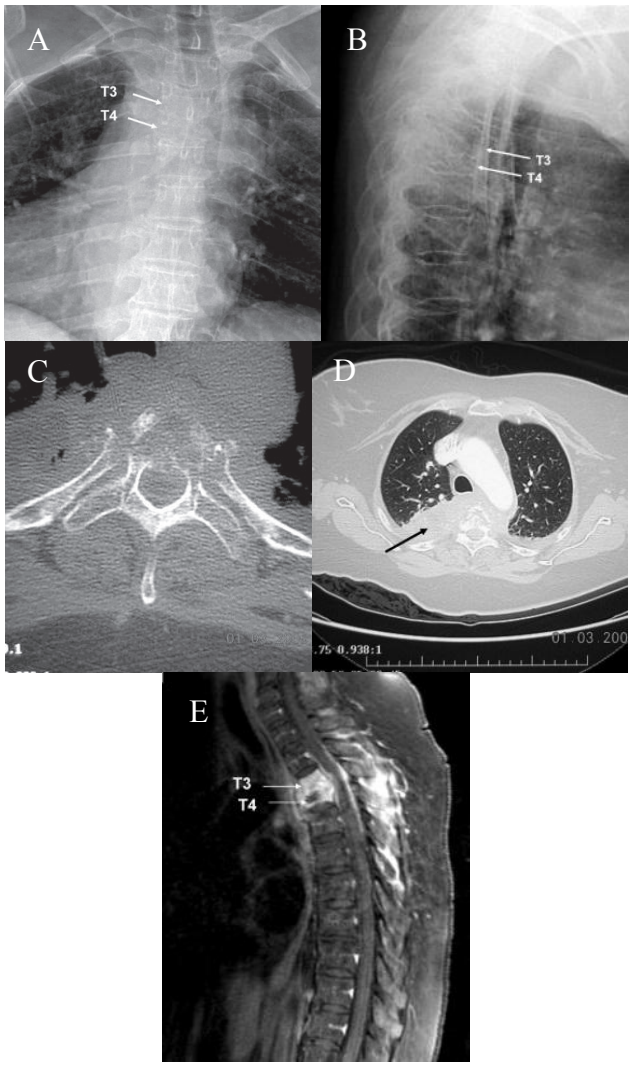

Figure 1. Preoperative images of the thoracic spine of a 68-year-old female patient who presented with a one-month history of progressive upper back pain and paresis. The AP (A) and lateral (B) radiographs show kyphotic collapse of the T3 and T4 vertebral bodies and intervening disk space. The CT scan (C and D) shows the lytic destruction of the vertebral bodies and the presence of a paraspinal abscess that extends into the right mediastinum. Fat-suppressed MRI scan (E) shows inflammatory changes affecting the anterior and middle columns, and clearly demonstrates the extrinsic spinal cord compression caused by the abscess and retropulsed bone fragments.

Intraoperative cultures revealed growth of methicillin-sensitive *Staphylococcus aureus*. Histologic findings likewise were consistent with osteomyelitis. Intravenous (IV) nafcillin was continued, but was switched to daptomycin after a

week because of the development of skin rash presumably secondary to drug hypersensitivity. She was given systemic IV antibiotics for 6 weeks and placed on oral antibiotics for another 6 weeks.

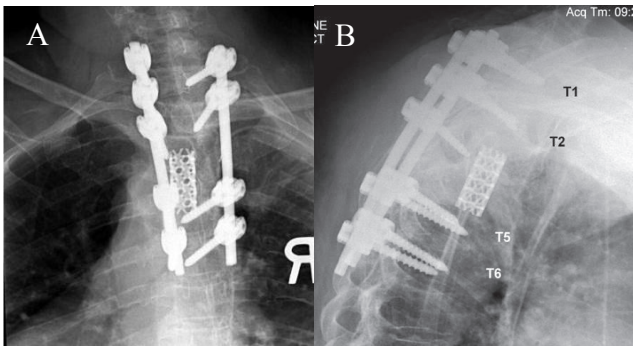

Figure 2. Immediate postoperative images. AP (A) and lateral (B) radiographs show placement of a titanium cage anteriorly spanning the T2 inferior endplate to the T5 superior endplate. Posterior instrumentation in the form a pedicle screw and rod construct from T1 to T6 is likewise evident. Kyphotic angle from T1 to T6 is 20 degrees.

At 6-month follow-up, she was already ambulating with a cane in her right hand, with no tenderness over her upper back, a completely healed skin incision, and 5/5 strength in both lower extremities. Radiographs showed her instrumentation to be stable. No development of proximal or distal junctional kyphosis was noted. These clinical and radiographic findings were maintained at her 1, 2 and 5-year follow-up assessments.

A CT scan performed 2 years (Figure 3) and repeated 5 years after surgery (Figure 4) confirmed successful posterior fusion from T1 to T6 and interbody fusion from T2 to T5. The sagittal alignment was well maintained. Spinal instrumentation was also intact and well fixed. Functional assessment at 5 years revealed an Oswestry Disability Index (ODI)[7,8] of 18 (a score indicating minimal disability) and a visual analog pain score (VAS) ranging from 2-4/10. The residual pain has not presented a hindrance in her work at the convent.

Discussion

While approval for the use of rhBMP-2 currently does not include cases of infection, there is emerging data on the effects of BMP on infection. Studies on the effect of BMP-7 (Osteogenic Protein-1 or OP-1) in animal models of infected fractures or nonunion showed that BMP-7 continued to enhance bone formation and fracture healing even in the presence of active infection.[9,10] Likewise, an important finding in the study by Govender et al. is a significant reduction in infection rate among Gustilo-Anderson type III fractures in the group treated with rhBMP-2. This is the first presented clinical evidence that rhBMP-2 does not increase the risk of developing an infection, and may in fact have a protective effect. The authors hypothesized that this effect may be due to the earlier achievement of fracture stability, or to the increased vascularity induced by rhBMP-2.[11] Our case report describes its utility and effectiveness in the setting of spinal infection.

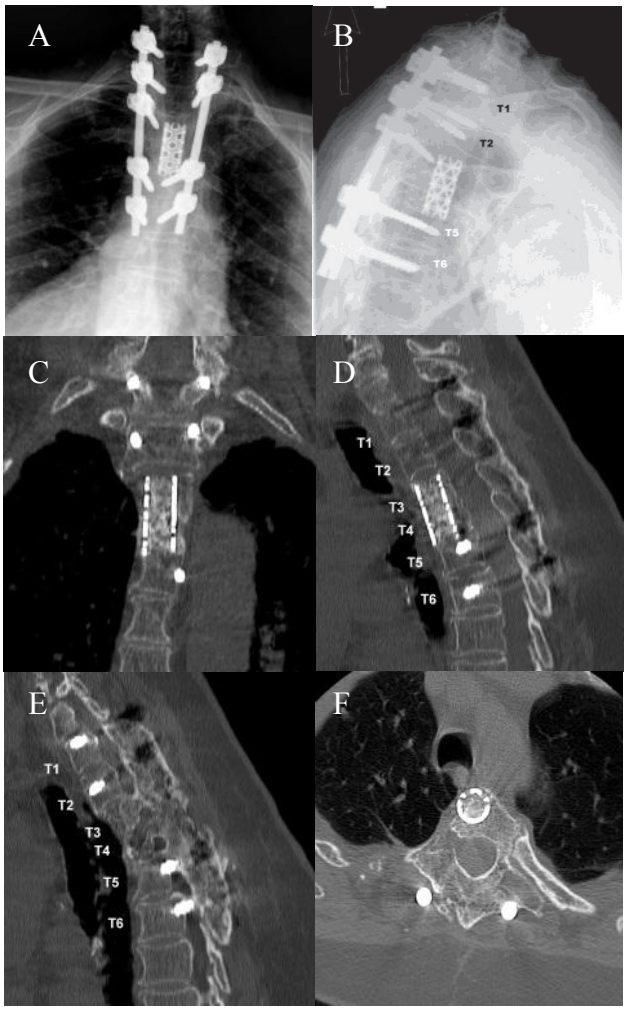

Figure 3. Two-year postoperative images. The AP (A) and lateral (B) radiographs show no evidence of hardware failure or loosening. There is also maintained kyphotic angle from T1 to T6 at 20 degrees. The CT scan images (coronal, C; sagittal, D and E; and axial, F) show evidence of good bone formation within the titanium cage and solid fusion below. While anterior fusion above the cage was unimpressive, likely secondary to retained disk material, there is evident robust posterior fusion from T1 down to T6. The axial cut also demonstrated the absence of the rib head on the right side from the costotransversectomy approach.

In 2007, Aryan et al. published a series of 15 cases of vertebral osteomyelitis all treated surgically with single-stage decompression, fusion, instrumentation, and

supplementation with rhBMP-2.[12] Of these, 6 cases involved the cervical spine, 5 thoracic, and 4 lumbar. After a mean follow-up period of 20 months, there was no case of recurrence of infection, and all cases went on to successful fusion, as demonstrated on x-ray or CT scan. Other reports showed uniform successful outcomes.[13-16] In the case we presented, fusion and eradication of infection were maintained five years after surgery.

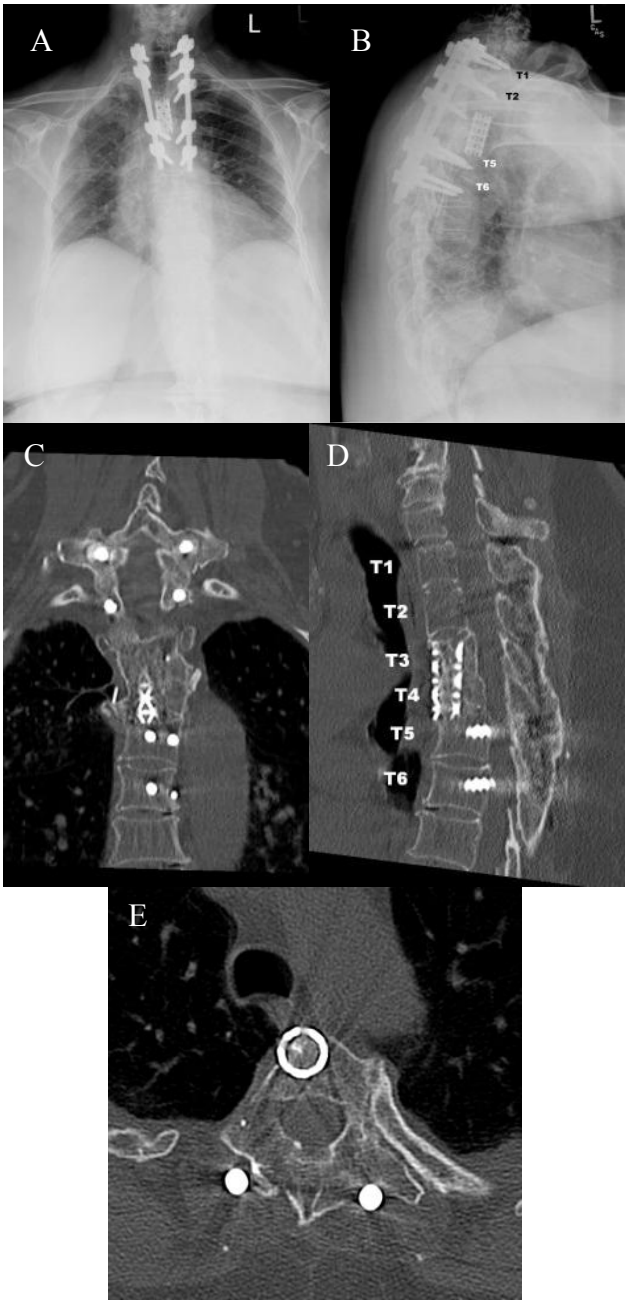

Figure 4. Five-year postoperative images. The AP (A) and lateral (B) show no hardware loosening and maintained kyphotic angle at 23 degrees. The CT scan images (coronal, C; sagittal, D and axial, E) show evidence of solid fusion.

There is understandable concern that any foreign material, including allograft and non-vascularized autograft, may decrease antibiotic effectiveness and increase glycocalyx formation when placed on an infected tissue bed. However, titanium has been shown to be less prone to bacterial colonization than either polymethylmethacrylate or stainless steel.[17] This theoretically makes it a better choice of material for use in infection. Published clinical studies have provided further evidence to this hypothesis.[16,18-20] Furthermore, in a case report on a retrieved titanium cage that was implanted for a 2-level corpectomy, Klemme et al. have clearly demonstrated impressive capability for osteosynthesis and bone remodeling within these cages.[21]

We report on the successful use of rhBMP-2 to promote fusion in the setting of active pyogenic vertebral osteomyelitis with maintained excellent clinical outcome at 5 years. This further adds to the growing evidence of its safety and efficacy in the treatment of bone infections. All of this information provides suggestive evidence that use of BMP in a spinal infection setting may be doubly advantageous—improving bone healing and helping to eradicate the infection.

References

1. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ. Hematogenous pyogenic spinal infections and their surgical management. Spine (Phila Pa 1976). 2000; 25(13):1668-79.
2. Rezai AR, Woo HH, Errico TJ, Cooper PR. Contemporary management of spinal osteomyelitis. Neurosurgery. 1999; 44(5):1018-25; discussion 1025-6.
3. Chan CT, Gold WL. Intramedullary abscess of the spinal cord in the antibiotic era: clinical features, microbial etiologies, trends in pathogenesis, and outcomes. Clin Infect Dis. 1998; 27(3):619-6.
4. Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. Neurosurg Rev. 2000; 23(4):175-204; discussion 205.
5. Hsieh PC, Wienecke RJ, O'Shaughnessy BA, Koski TR, Ondra SL. Surgical strategies for vertebral osteomyelitis and epidural abscess. Neurosurg Focus. 2004; 17(6):E4.
6. Urist MR. Bone: formation by autoinduction. Science. 1965; 150(3698):893-9.
7. Fritz JM, Irrgang JJ. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. Phys Ther. 2001; 81(2):776-88.
8. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000; 25(22):2940-52; discussion 2952.
9. Chen X, Kidder LS, Lew WD. Osteogenic protein-1 induced bone formation in an infected segmental defect in the rat femur. J Orthop Res. 2002; 20(1):142-50.
10. Chen X, Schmidt AH, Tsukayama DT, Bourgeault CA, Lew WD. Recombinant human osteogenic protein-1 induces bone formation in a chronically infected, internally stabilized segmental defect in the rat femur. J Bone Joint Surg Am. 2006; 88(7):1510-23.
11. Govender S, Csimma C, Genant HK, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am. 2002; 84-A(12):2123-2134.
12. Aryan HE, Lu DC, Acosta FL Jr., Ames CP. Corpectomy followed by the placement of instrumentation with titanium cages and recombinant human bone morphogenetic protein-2 for vertebral osteomyelitis. J Neurosurg Spine. 2007; 6(1):23-30.

13. Allen RT, Lee YP, Stimson E, Garfin SR. Bone morphogenetic protein-2 (BMP-2) in the treatment of pyogenic vertebral osteomyelitis. Spine (Phila Pa 1976). 2007; 32(26):2996-3006.
14. O'Shaughnessy BA, Kuklo TR, Ondra SL. Surgical treatment of vertebral osteomyelitis with recombinant human bone morphogenetic protein-2. Spine (Phila Pa 1976). 2008; 33(5):E132-9.
15. Ruf M, Stoltze D, Merk HR, Ames M, Harms J. Treatment of vertebral osteomyelitis by radical debridement and stabilization using titanium mesh cages. Spine (Phila Pa 1976). 2007; 32(9):E275-80.
16. Kuklo TR, Potter BK, Bell RS, Moquin RR, Rosner MK. Single-stage treatment of pyogenic spinal infection with titanium mesh cages. J Spinal Disord Tech. 2006; 19(5):376-82.
17. Chang CC, Merritt K. Infection at the site of implanted materials with and without preadhered bacteria. J Orthop Res. 1994; 12(4):526-31.
18. Fayazi AH, Ludwig SC, Dabbah M, Bryan Butler R, Gelb DE. Preliminary results of staged anterior debridement and reconstruction using titanium mesh cages in the treatment of thoracolumbar vertebral osteomyelitis. Spine J. 2004; 4(4):388-95.
19. Hee HT, Majd ME, Holt RT, Pienkowski D. Better treatment of vertebral osteomyelitis using posterior stabilization and titanium mesh cages. J Spinal Disord Tech. 2002; 15(2):149-56; discussion 156.
20. Liljenqvist U, Lerner T, Bullmann V, Hackenberg L, Halm H, Winkelmann W. Titanium cages in the surgical treatment of severe vertebral osteomyelitis. Eur Spine J. 2003; 12(6):606-12.
21. Klemme WR, Cunningham BW, Polly LD DW Jr. Microradiographic and histopathologic findings in a human cage explant after two-level corpectomy: a case report. Spine (Phila Pa 1976). 2002; 27(1):E15-7.