

# Spinal neuromodulation as a novel surgical option for failed back surgery syndrome following rhBMP exuberant bony growth in instrumented lumbar fusion: A case report and literature review

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## Abstract

**Background:** Bone morphogenetic protein (BMP) for instrumented lumbar fusion was approved in 2002, and since then has led to an increasing incidence of BMP-related neuropathic pain. These patients are usually resistant to conventional medical therapy and frequently undergo multiple surgical revisions without any pain relief.

**Case Description:** A 58-year-old male was referred to the author's outpatient clinic after four lumbar surgeries did not provide satisfactory pain relief. During his 10 years of suffering from low back pain after an injury, the patient was resistant to conventional and interventional treatment options. He was experiencing severe back pain rated 10/10, as well as right lower extremity pain, numbness, tingling, and motor deficits. Outside spine specialists had performed revision surgeries for BMP-related exuberant bone formation at L5–S1, which included the removal of the ipsilateral hardware and debridement of intradiscal and intraforamina heterotrophic exuberant bony formation. The author implanted the patient with a permanent continuous spinal cord stimulator, after which he achieved complete pain relief (0/10) and restoration of motor, sensory, autonomic, and sphincter functions.

**Conclusion:** This is the first reported case of restorative function with neuromodulation therapy in a BMP-induced postoperative complication, which is considered as a primarily inflammatory process, rather than nerve root compression due to exuberant bony formation. We hypothesize that neuromodulation may enhance blood flow and interfere with inflammatory processes, in addition to functioning by the accepted gate control theory mechanism. The neuromodulation therapy should be strongly considered as a therapeutic approach, even with confirmed BMP-induced postoperative radiculitis, rather than proposing multiple surgical revisions.

**Key Words:** Bone morphogenetic protein, exuberant bony formation, failed-back surgery syndrome, instrumented lumbar fusion, neuromodulation

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## INTRODUCTION

Since the introduction of recombinant human bone morphogenetic protein (rhBMP), there is a growing number of patients suffering from neuropathic pain as a result of local BMP-related nerve root compression by exuberant bony formation and localized inflammatory processes. At present, there are no good therapeutic options for relief of these patients' suffering. The introduction of rhBMP (InFUSE, Medtronic Sofamor Danek, Memphis, TN, USA) did not anticipate the fact that the new bone formation would continue to grow without regard to nearby neurological structures. The new bone formation can be found at the disk level within foraminal structures and can continue to grow with a vengeance. These locations are notoriously difficult to access surgically, and the surgical removal of exuberant bony formation is extremely challenging.

Bone morphogenetic proteins are multifunctional growth factors that were originally identified in the 1960s.<sup>[27,30]</sup> Urist *et al.* showed that BMP could be extracted from animal cortical bone by digestion of the demineralized cortical bone matrix with bacterial enzymes-collagenase.<sup>[26]</sup> A clinical use of recombinant human BMP (rhBMP) soon became available. Since then, BMP has been studied in the fields of dental, orthopedic, and back surgeries.<sup>[26]</sup>

In 2002, the Food and Drug Administration approved InFUSE Bone/LT-CAGE™ Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, TN, USA) as a recombinant human bone morphogenetic protein-2 [rh-BMP-2] solution with a carrier for the BMP solution (an absorbable collagen sponge made of bovine type I collagen) and a temporary metallic tapered spinal fusion cage.<sup>[28]</sup> The device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4–S1.<sup>[28]</sup> However, the use of rhBMP showed a significant increase, with more than 50% of anterior lumbar interbody fusion (ALIF) rhBMP use and approximately 43% of posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) use (not approved by FDA) by 2006.<sup>[22]</sup> Furthermore, cervical spine fusions with off-label rhBMP were performed.<sup>[7]</sup> The results of several small industry-sponsored studies suggested a BMP-related adverse event rate of <0.5% among 780 patients receiving rhBMP.<sup>[2-7,9-12]</sup> In 2008, the FDA issued a Public Health Notification stating that the off-label or unapproved uses of rhBMP can lead to life-threatening complications.<sup>[8]</sup> Depending on the anatomical fusion level, complications such as respiratory compromise due to tissue swelling, dysphasia, hoarseness, seroma, or hematoma are commonly encountered at the anterior cervical spine;<sup>[7,25]</sup> the lumbar spine fusion with rh-BMP tends to raise significant concerns for postoperative radiculitis (especially with off-label BMP use), retrograde

ejaculation, new or worsening nerve injury, and last but not least, heterotopic bone formation.<sup>[7,25]</sup> Heterotopic ossification compressing neural elements within the spinal canal and neural foramina has become an identified concern, with poorly documented treatment options.<sup>[7,25]</sup> One of the major causes is the use of off-label PLIF and TLIF.<sup>[7,25]</sup>

Treatment for heterotopic ossification and BMP-related radiculitis includes revision decompression surgeries, epidural steroid injections, and high doses of opioid medications often with marginal improvement or none at all.<sup>[29]</sup>

We report, for the first time, the benefits of spinal neuromodulation using a spinal cord stimulator therapy to successfully alleviate and relieve neuropathic pain caused by rhBMP-induced exuberant bony formation.

## CASE PRESENTATION

A 58-year-old right hand-dominant gentleman presented to the author's outpatient pain clinic with a persistent severe low back pain and right lower extremity pain, numbness, tingling, and partial right foot drop which did not improve with conservative treatment and four back surgeries. The patient rated his pain as 10 out of 10 on an 11-point verbal pain rating scale. He described his pain as burning, sharp, shooting, stabbing, deep pain, increased by lifting, climbing, straining, sitting, walking, sneezing, and present even at rest. The patient had a history of uncontrolled insulin-dependent diabetes mellitus with the last measured blood glucose value of 273 mg/dL and hemoglobin A1c (HA1C) of 9.3%. In addition, he had tinnitus, erectile dysfunction, hypercholesterolemia, history of chronic pain syndrome, and chronic narcotic dependency. The review of organ systems was not significant for other conditions.

Physical exam was notable for a positive straight right leg raise at 5°; there was significant neuropathy below the knees and below the ankles bilaterally. Allodynia was noted in the right L5 nerve root distribution and a right foot drop with 3/5 strength on dorsiflexion was identified. Back flexibility was limited due to pain in both flexion (35°), and extension (10°). Walk was feasible with mild limping presence, however, no walking-assist devices were used.

He previously sustained a work-related injury approximately 10 years ago that presented with low back pain and radiculopathy. Initially, he presented to his primary care physician with symptoms of right, more than left lower extremity numbness, tingling, and radicular pain which followed the pattern of the L5 and S1 nerve root distributions. At that time, the magnetic resonance imaging (MRI) of his lumbar spine showed a mild disk bulge at the L5–S1 level, and no other

significant findings. The patient underwent conservative treatment modalities over the course of several years, including physical therapy (multiple 6–10 week courses), myriad local/epidural/facet injections, and lumbar medial branch radiofrequency nerve ablations (>100), and increasing doses of narcotic medications (Hydrocodone–Acetaminophen: Sometimes even up to 12 pills a day, Morphine sulfate and Hydromorphone); all with minimal sustained relief. His quality of life started to deteriorate, his marital, social, and work life were greatly suffering and he discontinued his employment as a technician.

Surgical spine intervention was advised by other spine specialists which led to four surgeries in different hospitals as followed chronologically below during a period of five years. The first surgery consisted of right L5 hemilaminectomy, right L5–S1 foraminotomy with decompression of the nerve roots and microdiscectomy. Despite the surgery, right leg pain persisted. Several months post-surgery, a computed tomography (CT) scan of the lumbar spine with contrast showed mild disc bulges at L5–S1, left neural foraminal narrowing at the L4–L5 and L5–S1 levels and right L5–S1 foraminal narrowing [Figure 1a and b].

The second surgery was performed after an extensive history and imaging work-up during a 1-year follow-up. Surgery completed a revision of the right L5–S1 discectomy and foraminotomy. The right L5–S1 nerve root was decompressed from the scar tissue of his previous surgery seen on MRI [Figure 1c and d].

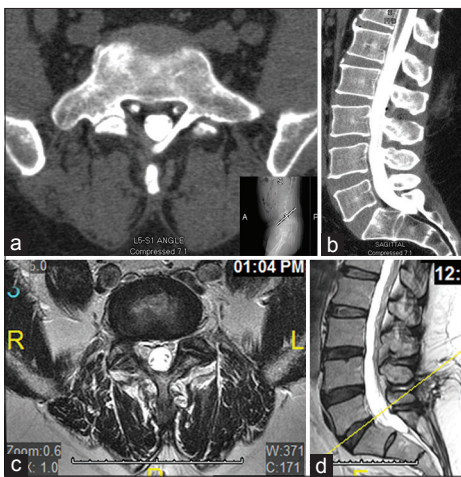
The third surgery proceeded with an instrumented spinal fusion, which was based on left L5 laminar fracture, right L5 spondylolitic defect around the area of previous foraminotomy, and current L5 laminectomy. An

instrumented fusion was accomplished using Legacy 5.5 rod system, allograft InFUSE (Medtronic Sofamor Danek, Memphis, TN, USA) with a transforaminal lumbar interbody fusion approach (TLIF). Despite the surgery, the patient had persistent pain at the right, more than left lower extremity, and lower back pain. His pain was 10 out of 10 and his quality of life continued to deteriorate thereafter. The patient was educated regarding behavioral modification programs and coping mechanisms.

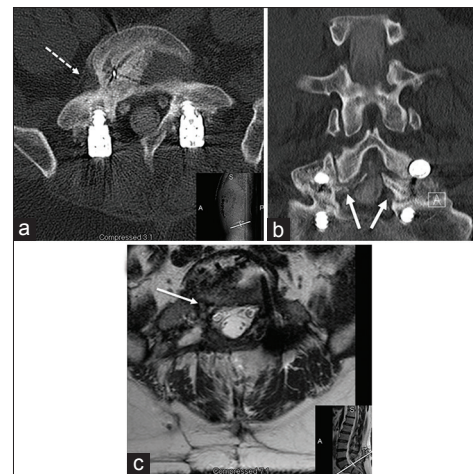
On subsequent follow-up imaging studies after the third spine surgery, exuberant bony formation [Figure 2a and b] was found and narrowing of the L5–S1 right foramina with nerve root compression [Figure 2c] and probable arachnoiditis. The fourth surgery was scheduled to remove the right-sided exuberant foraminal bony formation at L5–S1. An optimal widening of the right foramina required a removal of ipsilateral screw and other right-side instrumented fusion hardware [Figure 3a and b]. During a period of 5 years and four spine surgeries, the patient’s condition worsened, despite all what was done, even following the final revision surgery.

**Pre-neuromodulation procedure work-up**

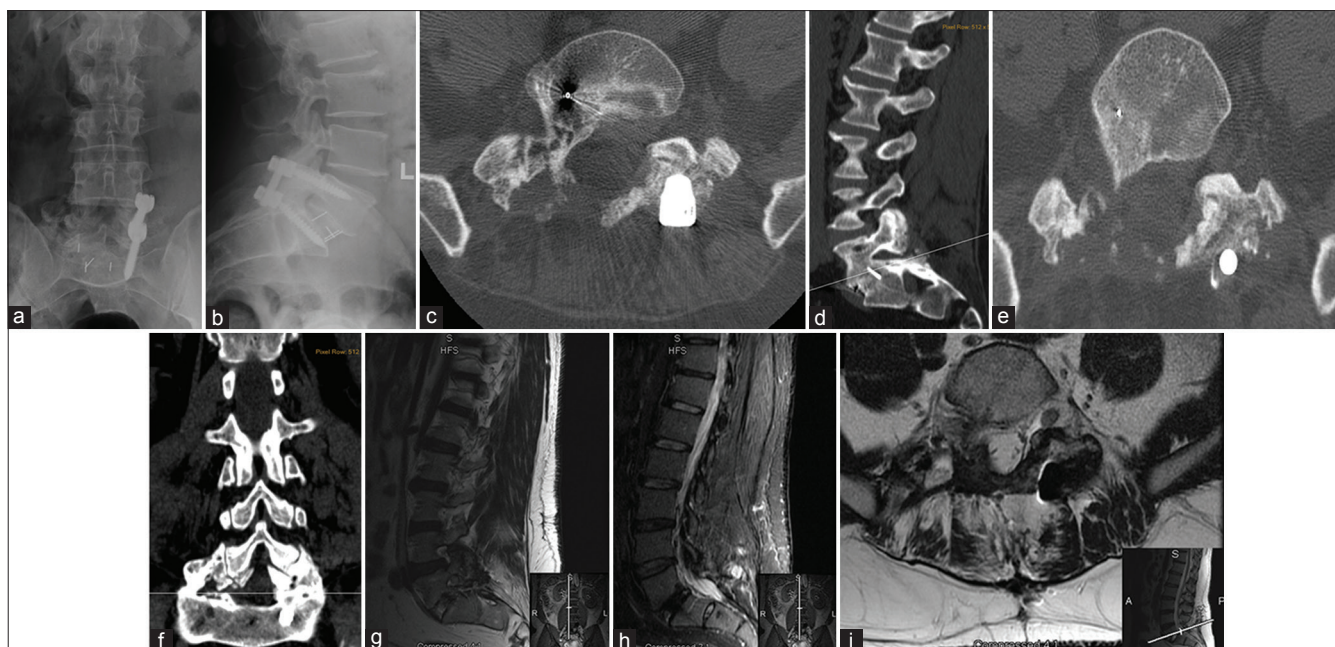
The patient was referred to the author for a second opinion. Before proceeding with the spinal cord stimulator (SCS) trial, the patient was referred to his primary care physician for education on diet, lifestyle, and management of his high serum blood glucose. In addition, the pre-surgical psychiatric evaluation confirmed appropriate



**Figure 1: Imaging study after first surgery (right hemi-laminectomy and foraminotomy at L5–S1).** Lumbar computed tomography (CT) myelogram during several month follow-up; (a) Transverse plane view at L5–S1; (b) Sagittal plane view. Lumbar Magnetic resonance imaging (MRI) during a 1-year follow-up; (c) Transverse plane view at L5–S1; (d) Sagittal plane view



**Figure 2: Imaging studies after third surgery (approximately 2 years after first surgery):** An L5–S1 instrumented lumbar spine fusion with bilateral rod placement. Lumbar computed tomography (CT); (a) Transverse plane view at L5–S1 with BMP-induced exuberant intradiscal and intraforamina bony formation (white-dash arrow); (b) Coronal plane view with early encroachment of foramen bilaterally (white arrows); (c) Lumbar MRI at L5–S1 (transverse plane view) with evidence of heterotopic ossification at L5–S1. One-third and two-thirds of right L5–S1 neuroforamina occupied by exuberant bony growth. Progressive nerve root disfigurement (white arrow) and intracanalicular and intradiscal encroachment due to BMP-related exuberant bony formation and failure of surgical drilling



**Figure 3:** Lumbar imaging studies after 4th surgery (approximately 5 years after 1st surgery) - removal of hardware on the right and drilling out to remove osteophytic, exhotropic, heterotopic, and myxotrophe bone. Lumbar X-ray; (a) Antero-posterior (AP) view; (b) Lateral view—hardware is in place with open R-sided foramen; heterotopic bone growth is entangling all around the nerve root in the facet. Lumbar computed tomography (CT) confirmed heterotopic bone growth reaches and was able to grow in difficult places; (c) Transverse plane view; (d) Sagittal plane view showing remaining bone and entanglement of the right S1-nerve root, intradiscal and intraforaminal without respect for neural elements; (e) Transverse plane view; (f) Coronal plane view demonstrating post-surgical drilling of the exuberant bony formation when compared to right and left sides; bone growth is in continuity with disc post-lumbar fusion; significant amount of bone is drilled out on the right when compared to the left. (g) Sagittal plane view (T2 sequence); (h) Sagittal plane view (STIR sequence); (i) Transverse plane view (T2 sequence) showing foramen of new bone with incomplete bone removal after right screw removal and surgical drilling

psychological aptitude for successful implantation of the SCS. Furthermore, the patient was slowly tapered down to a low dose of narcotic medications, until he was completely removed from his opioid treatment regimen, which was repeatedly confirmed with repeated urine toxicology screenings. A comprehensive study was performed with detailed evaluation of his previous images. Imaging studies revealed no cord compression or disc herniation. CT and MRI scans [Figure 3c-i] of the lumbosacral spine showed unilateral hardware at the left L5–S1; exuberant bony osteophyte formation with compressive elements occupying two-thirds of the right L5–S1 foramina; and impingement of the traversing nerve root; arachnoiditis, scarring, and postoperative changes.

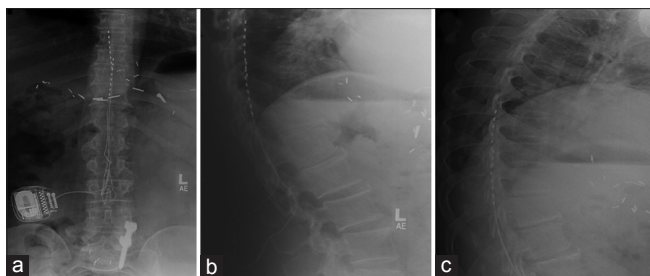
### Neuromodulation intervention

The author's standard policy with neuromodulation therapy allows patients to explore options of all major neurostimulator manufacturers (Boston Scientific, Medtronic, and St Jude Medical). The patient's preference was Medtronic's neurostimulator (Medtronic, INC, Minneapolis, MN, USA) that would permit future MRI utilization (Vectris SureScan MRI leads and SureScan MRI neurostimulator) and accommodate to changing body positions (RestoreSensor neurostimulator). A temporary trial using Medtronic percutaneous surgical leads was performed with proximal

contacts at T9–T10. The trial was successful with an immediate pain reduction to 4 out of 10 from his baseline of 10 out of 10. Pleased with the trial outcome, the patient was implanted with the permanent double Medtronic Vectris SureScan MRI percutaneous leads at T8–T10 level, and connected to the IGP generator with a RestoreSensor SureScan MRI neurostimulator [Figure 4a and b].

### Neuromodulation outcome

At the second year follow-up after neuromodulation therapy, the patient reported complete resolution of his low back pain and radicular symptoms with a consistent pain score of 0 out of 10. Furthermore, a complete restoration of motor, sensory, autonomic, and sphincteric function was observed using a continuous neurostimulator mode with a required 2-week generator recharge. The patient has been fully engaged in social activities as his mood and sleep have improved, and has reported an improvement of his marital relationship because erectile dysfunction has resolved. He has been weaned-off of all narcotics, neuropathic medications, and over the counter pain medications. Over the course of the neuromodulation therapy, he had not noted any fever, erythema, drainage, or swelling, and follow-up X-ray confirmed the placement of the leads without migration [Figure 4c]. He also reported an improved blood sugar control at less than 150 mg/



**Figure 4: Lumbar X-ray after Spinal Cord Stimulator (SCS) implantation; (a) Anterior-posterior view showing lead placement in T8–T10 connected to the IPG generator with restore-sensor on the right; (b) Lateral view confirms leads position in the epidural space; (c) Lumbar X-ray at 2 months after SCS implantation with lateral views confirming position of leads in the epidural space and placement at T8–T10**

dL on metformin alone and continues being monitored closely by his primary care physician.

## DISCUSSION

This case of multiple failed surgical spine fusions demonstrates a challenging scenario resulting from the pathophysiology of BMP-related complications (soft tissue swelling, postoperative radiculitis, and ectopic bone formation) that persisted in spite of numerous surgical revisions. A complete restoration of motor-sensory function with neuromodulation therapy, which is not considered to be a corrective procedure, should prompt further investigation to explain the complex mechanism of action of a SCS. We can hypothesize that the inflammatory process plays a vital etiologic role<sup>[25]</sup> rather than a compressive etiology of BMP-induced exuberant bony formation.<sup>[14]</sup> Therefore, we can speculate that neuromodulation may interfere with the inflammatory processes by regulating local blood flow and release of neuroendocrine modulators. Perhaps an early neuromodulation intervention should be considered in a confirmed BMP-induced postoperative neuropathic pain and motor dysfunction, which might serve as an essential alternative to multiple surgical spine revisions. Since the introduction of rhBMP spinal fusion, we are presenting the first example of a non-surgical modality providing a restorative motor function and pain relief with neuromodulation therapy.

The exact mechanism of action of our treatment modality is difficult to determine. It has been hypothesized that continued nerve stimulation may increase blood flow, thereby minimizing potential ischemic insult and radicular symptoms associated with impingement.<sup>[17-19]</sup> The concept of the “gate control theory” provides a more sophisticated explanation, which takes into consideration the selective inhibition and desensitization of the abnormal circuits.<sup>[20]</sup> However, this theory is incomplete and does not fully explain the lack of uniformity in pain

modulation between nociceptive and non-nociceptive pain.<sup>[1]</sup> It is known that the SCS device stimulates several structures (the dorsal column, lateral funicular, and dorsal root fibers) by creating an electric field along the dorsal column fibers with subsequent inhibition in pain transmission in the ascending nociceptive pathway and activation of the descending anti-nociceptive pathways.<sup>[23]</sup>

The efficacy and cost-effectiveness of a treatment method is an indisputable and important aspect in current clinical decision-making. Even so, while neuromodulation is not considered to be a corrective procedure, it is evident that an excellent symptom pain relief can be achieved in structurally-related lumbar injuries. North *et al.* studied the effectiveness and cost analysis for SCS versus reoperation in failed-back surgery syndrome (FBSS), and it was found that most of the patients randomized into reoperation crossed-over to SCS; 13 out of 21 patients (62%), whereas in the SCS group only 5 out of 19 (26%) crossed-over to operation.<sup>[21]</sup> In patients who were achieving long-term success outcomes with SCS, the cost per patient was \$48,357 compared to \$105,928 per patient in long-term success outcomes with reoperation. Short-term successful outcome did not provide any significant difference in the total cost between SCS or reoperation. Cost-effectiveness of SCS was achieved when patients declined repeated surgery. The SCS therapy was more effective and less expensive when compared to reoperation in FBSS patients. Thus, the authors concluded that SCS should be the first therapy of choice among FBSS patients.<sup>[21]</sup>

FBSS is a term commonly used to describe patients that, despite spine surgery, (laminectomy, discectomy, fusion) continue to have persistent back and/or leg pain.<sup>[24]</sup> The predictability of FBSS occurrence is outlined by pre, intra, and postoperative factors. The most important preoperative factor is the selection of appropriate candidates for spinal surgery and a clear communication for postoperative expectation in terms of pain relief. The intraoperative factors include misdiagnosis, inadequate disc decompression, failed fusion, misplaced screw, and graft subsidence. Postoperative etiology of FBSS includes stenosis of the spinal canal or nerve roots, epidural fibrosis and scar tissue formation, and residual disk material.<sup>[24]</sup> Treatment of FBSS is accomplished after detailed and complete imaging studies (MRI, X-ray, discography, CT with multiplanar reconstructions, CT myelogram). Available therapeutic options include interventional procedures, pharmacological, and interdisciplinary management.<sup>[13]</sup>

Our patient underwent extensive imaging studies and a multimodal treatment approach with complete pain resolution only after SCS implantation. This outcome may confirm the findings from studies on FBSS treatment, which compared the use of an SCS with conventional

medical therapy (CMM) or repeat spine surgery.<sup>[15,16,21]</sup> Kumar *et al.* found that SCS provided significant pain relief and improved the health-related quality of life and functional capacity in patients with neuropathic pain secondary to FBSS, whereas patients in the CMM group had little or no pain relief ( $P < 0.001$  at 6 months and  $P = 0.03$  at 12 months follow-up).<sup>[15]</sup> At the 24-month follow-up, the pain relief was sustained in 42 out of 52 patients randomized to SCS group and was significantly improved compared to the baseline scores ( $P < 0.0001$ ). The Oswestry disability index ( $P = 0.0002$ ), short-form health survey-36 ( $P < 0.01$ ), and euroQoL-5D instrument ( $P < 0.0001$ ) showed significant improvements among subjects in the SCS group. These findings further support the utilization of neuromodulation intervention for FBSS with the neuropathic component, as described in the case above.<sup>[16]</sup>

## CONCLUSION

A complete recovery of neurological function and complete resolution of pain symptoms was achieved with neuromodulation intervention after 10 years of unsuccessful surgical revisions and conservative medical therapy. An inflammatory process is the primary pathoetiological factor in this case of BMP-induced neuropathic pain rather than the compressive nature of BMP-induced heterotrophic bony formation. This theory is most consistent as this case demonstrates successful symptom resolution with neuromodulation therapy and discontinuing pain medications (narcotics and OTC) entirely. This is a much more attractive approach when compared with multiple surgical revisions and dependency on pharmaceutical therapies. Therefore, we believe that the spinal neuromodulation should be a procedure of choice with confirmed BMP-related neuropathic pain.

### Presentation at a meeting

Organization: North American Society of Neuromodulation (NANS) 19<sup>th</sup> Annual Meeting, Las Vegas, 10 December, 2015.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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