Imaging symptomatic bone morphogenetic protein-2–induced heterotopic bone formation within the spinal canal: case report

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Heterotopic bone formation within the spinal canal is a known complication of bone morphogenetic protein–2 (BMP-2) and presents a clinical and surgical challenge. Imaging modalities are routinely used for operative planning in this setting. Here, the authors present the case of a 59-year-old woman with cauda equina syndrome following intraoperative BMP-2 administration. Plain film myelographic studies showed a region of severe stenosis that was underappreciated on CT myelography due to a heterotopic bony lesion mimicking the dorsal aspect of a circumferentially patent thecal sac. When evaluating spinal stenosis under these circumstances, it is important to carefully consider plain myelographic images in addition to postmyelography CT images as the latter may underestimate the true degree of stenosis due to the potentially similar radiographic appearances of evolving BMP-2–induced heterotopic bone and intrathecal contrast. Alternatively, comparison of sequentially acquired noncontrast CT scans with CT myelographic images may also assist in distinguishing BMP-2–induced heterotopic bone lesions from the thecal sac. Further studies are needed to elucidate the roles of the available imaging techniques in this setting and to characterize the connection between the radiographic and histological appearances of BMP-2–induced heterotopic bone.

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KEY WORDS BMP-2; myelography; heterotopic bone; spinal stenosis; technique

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ABBREVIATIONS BMP-2 = bone morphogenetic protein–2; PSO = pedicle subtraction osteotomy.
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We assert that plain film myelography may nevertheless continue to play a valuable role in the workup of spinal stenosis. For example, there may be scenarios in which this technique provides information not seen, or perhaps misinterpreted, on CT myelography. As a stand-alone modality, CT scanning is not without its own limitations. The artifacts of metallic hardware, for instance, frequently complicate the interpretation of CT images. In addition, we hypothesize that in the setting of BMP-2–induced spinal stenosis, the heterogeneous radiodensity and morphology of evolving heterotopic bony tissue may confound adequate characterization of these lesions, especially in relation to the normal bony structures and other elements of the neuraxis with overlapping radiodensities. Furthermore, the potential emergence of multiple sites of heterotopic bony growth at different time points may also pose challenges to the interpretation of these attenuation-based imaging modalities. Whatever else, imaging studies will undoubtedly remain central to the management of both the anticipated and unanticipated sequelae of spine surgery. At present, the optimal imaging modality for BMP-2–induced heterotopic bone growth has yet to be established.

Case Report

Here we present the complex case of a 59-year-old woman with an extensive history of spinal surgeries. The patient had a history of right knee and hip arthroplasty, venous thromboembolism necessitating the placement of an inferior vena cava filter, obstructive sleep apnea on home oxygen, and prior tobacco use. Before coming under the care of the present group, the patient had already undergone at least 10 surgical procedures on her spine for a history of flat-back syndrome, culminating in the implantation of a T2-pelvic construct at an outside hospital. One year before presenting to the current neurosurgical service, the patient developed pseudarthrosis at the L2–3 level, with the primary symptom of low-back pain, and this problem was treated with an instrumented lateral interbody fusion (lateral plate spanning L2–3) with removal of the posterior hardware distal to L-1 by the neurosurgical service of an outside hospital. Following this, the patient experienced improvement in her symptoms for over a year but subsequently presented to the current neurosurgical group with intractable low-back pain, a profoundly positive sagittal balance, and urinary incontinence. She was admitted to the hospital after CT imaging showed an insufficiency fracture through the sacrum and pseudarthrosis at L3–4 with lumbar kyphosis.

The patient was subsequently scheduled to undergo correction of her spinal deformity with L-1 pedicle subtraction osteotomy (PSO) to address the positive sagittal balance and revision of her existing hardware construct with extension of the instrumentation back down to the pelvis to treat her sacral insufficiency fracture (Fig. 1). One large pack of BMP-2 was used for the entire procedure (12 mg total) with the matrix sponge divided into 4 roughly equal pieces. Two of the BMP-2–bearing matrix sponges were placed posterolaterally at the level of the PSO site while the other 2 fragments were placed in the vicinity of the sacral insufficiency fracture, at the level of S-1. In addition to the BMP-2, morcellized autograft and allograft materials were placed posterolaterally from the vicinity of the PSO site down to the sacrum.

At 6 weeks postoperatively, the patient’s sacral pain had resolved and she reported improvement in her bowel and bladder symptoms. She was able to stand up straight and had relinquished use of her walker. By 4 months postoperatively the patient continued to report improvement in strength of her lower extremities bilaterally. Unfortunately, however, she also noted burning paresthesias of the lower extremities as well as a return and worsening of urinary and bowel incontinence at this time. The patient presented to the emergency department for these symptoms, at which point conventional and myelographic studies were acquired to assess for possible spinal stenosis or another explanation of her symptoms.

The CT myelogram itself was relatively unremarkable with the exception of the fact that there appeared to be some lack of dye flowing through the anterior portion of the thecal sac at the site of the osteotomy, and therefore the decision was made to proceed with an explorative surgery to address any bone growth that might have been present at this site. Intraoperatively, extensive heterotopic bone was encountered in the spinal canal, and this bone turned out to be most consistent with what was seen on the plain myelography images rather than the CT myelography images, as the majority of the heterotopic bone was located in the dorsal aspect of the spinal canal rather than in the anterior aspect. Fortunately, this heterotopic bone was capable of being removed without complication. Careful dissection was made, and a drill was passed through bone that appeared to be forming as a result of the fusion process with BMP-2. This fusion mass was whitish in appearance and of a somewhat softer consistency than the other bony elements. A plane was developed between the dura and the fusion mass, and partial L-1 and L-2 repeat laminectomies were performed. Further dissection of the dura...
away from the fusion mass was then performed, such that bilateral L1–2 medial facetectomies were performed, and bilateral L1–2 foraminotomies were performed to address the problem with the heterotopic bone.

A comparison of sagittal and axial CT images acquired immediately following the L-1 PSO with extension of instrumentation to the pelvis using BMP-2 4 months previously (Fig. 2A and B) and upon re-presentation with worsening paresthesias and incontinence (prior to undergoing the abovementioned exploratory surgery with L1–2 bilateral repeat partial laminectomies, facetectomies, and foraminotomies; Fig. 2C and D) demonstrates interval development of heterotopic bone in the spinal canal just distal to the level of the PSO site, that was underappreciated on the preoperative radiographic interpretation. Sequential axial CT myelograms at the level of stenosis acquired at the time of re-presentation are shown in Fig. 3. Complete obstruction of the flow of contrast within the thecal sac was not identified on these CT myelograms at this time, and the final interpretation was “moderate canal stenosis” at L1–2 with an otherwise circumferentially patent thecal sac at this level. Intraoperatively, however, as already noted, the degree of stenosis at this level was much more severe.

Looking back at the plain myelographic images, it is noted that these images showed much more severe stenosis and were thus more revealing of the true extent of the heterotopic ossification than the CT myelogram images (Fig. 4). What was thought to be contrast within the right posterolateral aspect of the thecal sac on the CT myelograms was more likely heterotopic bone compressing the thecal sac, and hence the degree of true stenosis was underinterpreted preoperatively on these tomographic images. Of note, neither the contrast settings nor the position of the workstation significantly altered the final interpretation of the CT myelograms. Taken together, Figs. 2–4 provide a relatively complete picture of the spinal and extraspinal morphology while clarifying the pattern of contrast movement within the thecal sac. Figure 2C clearly demonstrates that the lesion of interest does not simply represent dural herniation into the PSO site but rather represents spinal stenosis secondary to heterotopic bone, a lesion that was inadequately characterized on CT myelography in comparison with the plain films.

Unfortunately, although the patient otherwise retained full strength, she reported experiencing bowel and bladder incontinence yet again 2 years later, and therefore further myelographic studies of the cervical, thoracic, and lumbar spine were acquired, which demonstrated a large osteophytic process at C6–7. As this turned out to be a challenging lesion intraoperatively, a C-6 corpectomy was performed with insertion of a titanium cage and C5–7 anterior arthrodesis with a plating system. Interestingly, CT imaging of the neuraxis at this time showed interim healing of the patient’s sacral insufficiency fracture, possibly secondary to the effects of BMP-2. Twenty-two months after this episode, the patient presented with memory difficulty, intermittent headaches, confusion, balance difficulty, and continued urinary incontinence. As it was unclear as to whether this was a new or old condition, given her longstanding history of urinary incontinence, repeat myelographic studies were performed to rule out recurrent stenosis. No stenotic lesions were found; however, the opening pressure during the myelographic procedure was 17 cm H2O. A head CT scan showed right greater than left ventricular size, and therefore the patient underwent placement of a ventriculoperitoneal shunt for hydrocephalus. Ten months later the patient was admitted for hypercapnic respiratory failure, the differential of which included opiate overdose versus CO2 narcosis versus sepsis.

Discussion

Structural imaging techniques, including plain film radiography and CT scanning, are routinely acquired to assess alignment and vertebral fusion following spine surgery, while plain film myelography with or without the supplement of CT is routinely performed to assess suspected spinal cord impingement. MRI would be of use in assessing for compression of the nerve roots due to heterotopic bone but quite often image interpretation is at risk for being compromised by artifact from preexisting...
More recently investigators have used these and other modalities to characterize the efficacy of BMP-2 for promoting arthrodesis.2,8,18,20 BMP-2 has been used to promote fusion of the vertebral elements without the burden of autograft, and at present this agent is FDA approved for use in anterior lumbar interbody fusion. While attempts to identify optimal formulations and methods of delivery are ongoing, the use of BMP-2 in spine surgery remains controversial due to reports of safety issues.1,3,7,9,11,12,14,16,17 While the basic mechanisms underlying BMP-2–induced vertebral fusion and heterotopic ossification are largely understood,4–6,13,15 the parameters for optimal imaging of these complications are still being identified.

BMP-2 has been successfully used for more than 10 years in helping patients achieve desired fusion of the vertebral elements. Despite this success, however, complications may arise. While one can never be absolutely sure that the development of heterotopic bone in the spinal canal is due to BMP-2 alone, a combination of factors contribute to our certainty that it is responsible for this heterotopic growth, including 1) the coincidence between the site of intraoperative BMP-2 placement and the site of the stenotic lesion as seen intraoperatively, 2) our experience in using bone graft materials without BMP-2 and the lack of heterotopic lesions related to this, and 3) the existence of other case reports and basic science research establishing a connection between BMP-2 and heterotopic bone growth. In this communication we have sought to direct attention to a potential problem when imaging this complication and to offer some suggestions for overcoming it.

The case we have presented demonstrates the ongoing value of plain film myelography in assessing spinal cord impingement due to BMP-2–induced heterotopic bone growth within the spinal canal. In this instance the CT myelogram underestimated the degree of stenosis, perhaps as a result of the similar radiodensity of the intrathecal contrast and the heterotopic bone. We believe careful consideration of plain film myelography images is likely to be especially important in symptomatic cases during the early stages of bone formation in patients who have re-
ceived BMP-2, before extensive ossification of the heterotopic tissue has taken place. Alternatively, clinicians and surgeons may also consider the strategy of sequentially acquiring both conventional noncontrast CT as well as CT myelography in this specific setting, as a comparison of these images should help to clarify more exactly the irregular morphology of these heterotopic lesions in contradistinction to the thecal sac. We advocate for myelography in this patient population with close attention paid to the plain film studies. Further studies are required to elucidate the roles of the available imaging techniques in this setting and to clarify the spectrum of radiographic patterns resulting from BMP-2–induced heterotropic bone.

Unfortunately, a histological bony tissue sample was not sent for histological examination in this instance as the discrepancy between the plain film and CT myelograms was realized retrospectively following the revision surgery. However, this absence only highlights the need for a more rigorous comparison between the histological and radiographic appearances of BMP-2–induced heterotropic bone, an undertaking that will serve as the foundation for a future communication.

Conclusions

When performing myelographic studies to evaluate spinal pathology following the use of BMP-2, it is important to carefully evaluate the plain film images in addition to the postmyelogram CT images as the latter may underestimate the true degree of stenosis. Alternatively, comparison of sequentially acquired conventional noncontrast CT and CT myelography may also assist in distinguishing the contours of the heterotopic bony lesion from the boundary of the thecal sac.

References


Disclosures

Dr. Sansur reports that he is a consultant for Medtronic and DePuy Synthes.

Author Contributions

Conception and design: Sansur. Acquisition of data: Sansur, Chryssikos. Analysis and interpretation of data: all authors. Drafting the article: Chryssikos. Critically revising the article: all authors. Reviewed submitted version of manuscript: Chryssikos. Administrative/technical/material support: Sansur. Study supervision: Sansur.

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