The Journal of Turkish Spinal Surgery 2007; 18 (2): 25-29

OLGU SUNUMU / *CASE REPORT*

BONE MORPHOGENIC PROTEIN INDUCED HETEROTOPIC OSSIFICATION CAUSING SPINAL STENOSIS

SPİNAL STENOZA YOL AÇMIŞ KEMİK YAPISAL PROTEİNİ İLE İNDÜKLENMİŞ HETEROTOPİK OSSİFİKASYON

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SUMMARY:

Objectives: *To report a case of late neurologic compromise by heterotopic bone formation after use of human bone morphogenetic protein (rhBMP-2) in posterior lumbar interbody fusion (PLIF) procedure.*

Summary of background data: *Bone morphogenic proteins have been the subject of numerous research studies for the last decades. Although available evidence suggests that the use of bone morphogenic proteins to promote human spine fusion is effective and safe there are some concerns about the possibility of new bone formation proximal to neural structure. While new bone formation has been observed in PLIF cases, no neurological compromise have been reported to date.*

Methods: *38 year-old female patient with nerve root compression symptoms due to heterotopic bone formation induced by rhBMP-2 after the PLIF procedure is reported.*

Results: *Patients neurologic symptoms subsided after the removal of heterotopic bony tissue.*

Conclusion: *Bone morphogenic proteins are potent osteoinductive agents. Use of BMP could lead to heterotopic ossification with possible intracanal bone formation. The PLIF technique inherently requires a laminectomy and placement of the interbody device with close proximity of the neural tissues. Using bone morphogenic proteins with this technique should be approached with caution because of the possible intracanal new bone formation and unexpected neurologic compromise.*

Key words: *Bone morphogenic protein (BMP), heterotopic ossification, spinal stenosis*

Level of Evidence: *Case Report, Level IV*

ÖZET:

Posterior lomber cisimler arası füzyon (PLIF) uygulanan bir hastada insan morfojenik proteini (rhBMP2) kullanımı ile nörolojik bozulma oluşan bir olgunun sunulması amaçlanmıştır. Kemik morfojenik proteini son yıllarda üzerinde çok sayıda çalışma yapılan bir objedir. BMP'nın insanda güvenli ve etkili bir şekilde spinal fizyonu artırdığı yolundaki kanıtların olmasına rağmen, yeni kemik yapımının nöral dokulara bası yapabileceği endişesi de vardır. PLIF vakalarında yeni kemik yapımı görülmesine karşın, nörojik bozulma bugüne kadar rapor edilmemiştir. Burada rhBMP2 ile PLIF işlemi uygulandıktan sonra hetetropik kemik yapımı ile sinir kökü basısı olan 38 yaşında bayan hasta sunulmuştur. Heterotopik kemik, cerrahi olarak çıkartıldıktan sonra hastanın nörolojik bulguları düzelmiştir. BMP güçlü bir osteoindüktif ajandır. BMP kullanımı olası kanal içi kemik oluşumu ile heteropik ossifikasyona yol açabilir. PLIF tekniğinde geleneksel olarak laminektomi yapılır ve cisimler arası kafes nöral yapılarak yakın komşulukla yerleştirilir. Bu teknikle beraber BMP kullanımında, olası kanal içi yeni kemik yapımı ve tahmin edilemeyen nöral bozukluk açısından dikkatli olmak gereklidir.

Anahtar Kelimeler: *Kemik morfojenik proteini heterotopik assifikasyon, spinal stenoz.*

Kanıt Düzeyi: *Olgu Sunumu-Düzey IV*

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Introduction

The chronicle of the Bone morphogenic proteins (BMPs) began with Dr. Urist in 1965. Since that time, numerous investigators have contributed to the understanding of precise pathways for osteoinductive capability of these protein chains. In the past decade, two recombinant BMPs, rhBMP-2 (Medtronic Sofamor Danek) and OP-1 (Stryker Biotech) were manufactured using recombinant DNA biotechnology utilizing mammalian cells[16]. Numerous animal and human studies utilizing both of these BMP proteins have been performed. Safety and efficacy data are available for both rhBMP-2 and OP-1.[10,13,14]

A major concern about BMPs is the risk of heterotopic bone formation near neural structures which could lead to stenosis by bone overgrowth. While safety of rhBMP-2 in anterior spinal fusion and posterolateral fusion,[3,4,5,6,10] is well documented, the same cannot be said for posterior lumbar interbody fusion (PLIF). There is one clinical trial which studies PLIF with rhBMP-2 application but it has not been completed.1 Studies have shown that if BMP proteins or BMP carrier contacts the dura through a decompression site, new bone will form over the dura and may result in re-stenosis.[9,11,12] During the application of rhBMP-2 with PLIF technique, through site of posterior annulectomy, contact with neural elements is somewhat inevitable. However, to the best of our knowledge, there are no cases of neurological complications due to rhBMP-2 usage in spinal fusions reported in the literature. The goal of this paper is to present a case of heterotopic bone formation which caused foraminal narrowing and radicular symptoms after a PLIF procedure supplemented with rhBMP-2.

Case Report

We consulted on a 38 year-old female for a second opinion regarding persistent bilateral leg pain, right worse than left. She originally underwent L4 to S1 decompression with posterior lumbar interbody fusion, posterolateral fusion and instrumentation at another clinic in August of 2002. Initial diagnosis was degenerative disc disease with spinal stenosis at L4-5 and L5-S1. According to her operative note rhBMP-2 (INFUSE, Medtronic Sofamor-Danek) was used for both interbody fusion and posterolateral fusion. During the PLIF procedure, the right side allograft (Tangent Medtronic Sofamor-Danek) was placed first with subsequent placement of milled autografts and rhBMP-2 on the left side. Postoperatively, because of worsening right extremity dysesthesias, a new MRI and CT scan (February 2003) were obtained. These studies demonstrated a fluid collection at the laminectomy site (Fig 1). This was thought to be a CSF leak,

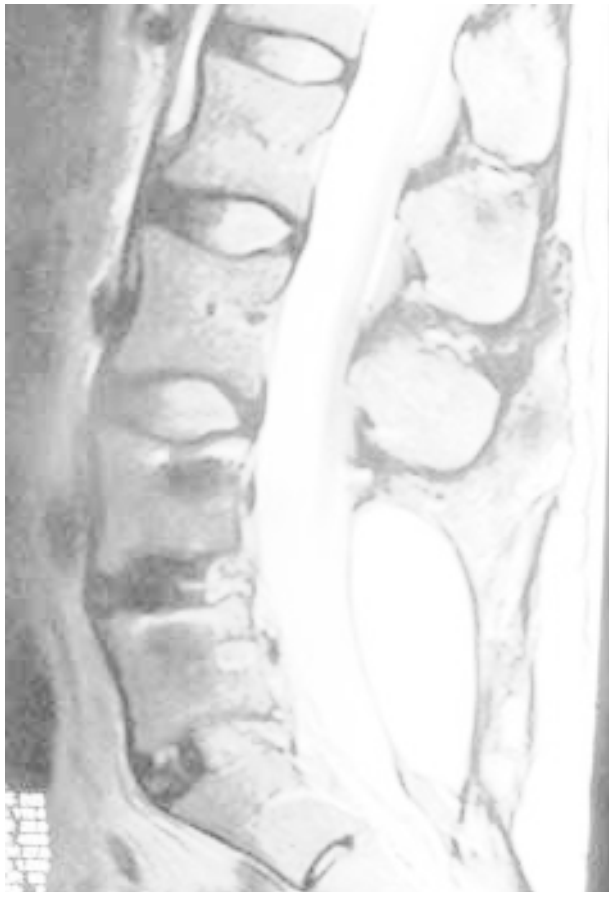

Figure 1. T2 weigthed sagittal image of the lumbosacral junction. Fluid collection behind the dura.

and the patient underwent evaluation of this pseudomeningocel and lumbar drain application to allow healing of the durotomy by the same surgeon at March of 2003. She continued having increasing paresthesias in the lower extremities especially right side. In June of 2003 patient presented to our clinic for second opinion regarding persistent bilateral leg pain, right worse than left. Pain present all the time and aggrevated with sitting and walking, better with lying down. On examination at the admission date, her leg pain was worse on the right than on left. She had normal erect posture but limited range of motion of the spine especially with forward flexion. She walked with a normal gait pattern but had weakness of EHL on the right side with a grade 4 out of 5 power. Also she had tenderness over the instrumentation with palpation. Straight leg raising was negative bilaterally. Radiographs showed a solid fusion from L4 to S1 with intact spinal instrumentation. A new CT-scan was ordered and demonstrated bilateral bizarre bone formation at the L4-5 level around the dural sac (Figure 2-4). Bone formation was more prominent right side than left (Fig-3-4). She subsequently underwent selective nerve root injections and had complete pain relief for a short while.

Patient was scheduled for removal of instrumentation and decompression. After the evacuation of hematoma, removal of posterior instrumentation, a right L4-5 foraminotomy was performed. During the foraminotomy significant amount of new bone formation was encountered in the foramen from the bony edges of the L4-5 interspace. It was still immature bone and was not a residual osteophyte from previous degenerative disc problems. The exiting L4 nerve root was identified into the foramen and it was noted to be stenotic. This immature, heterotopic bone was then freely readily removed with curettes and Kerrison rongeurs decompressing the L4 nerve root. Postoperatively, the radicular leg pain diminished significantly. She is now in her tenth postoperative month and except altered light touch sensation, she is symptom free. She returned to her work after six months.

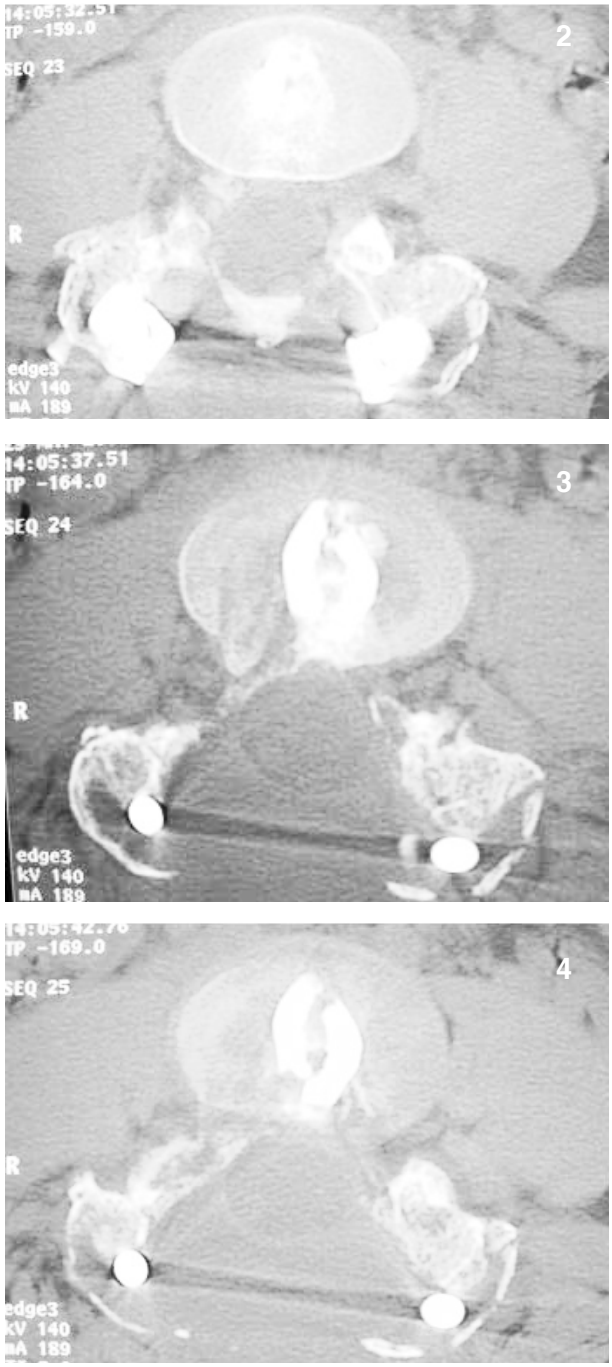

Figure-2,3,4. Sequentially three frames from down to up. Note the new bone formation on the right side.

Discussion

Experimental studies have shown that if BMPs contact a raw bone surface such as a laminectomy site or a decompressed neuroforamen in sufficient concentration, new bone and restenosis may develop.[9,11,13] However there is no report of canal or foraminal stenosis occurring after the use of rhBMP-2 for posterolateral spine fusion.[2,8,13] On the other hand, posterior lumbar interbody fusion technique inherently requires laminectomy and placement of interbody device with close proximity to the neural structures. Alexander and colleagues conducted a clinical trial of rhBMP-2 usage with PLIF technique1 and observed heterotopic bone formation in the spinal canal posterior to the fixation device and in the tract of their insertion. Despite this finding, no clinical sequelae were observed, and the study was halted before completion. Additionally, neurological sequela have not been reported in any other experimental or clinical studies.[1,9,11,12]

The pathway of the neural preservation is unclear but possible theory is that narrowing of the canal and foramina is limited by the mechanics of the cerebral spinal fluid pressure and pulsation.[7,13] In this case, a lumbar drain was used after evacuation of the pseudomeningocele. This drain could have decreased the cerebral spinal fluid pressure and therefore contributed to the pathologic pathway of the neurologic compromise based on pressure theory.

In our case intracanal heterotopic bone formation was observed at L4-5 level. Surprisingly, it was more prominent right side because rhBMP-2 had been placed from left side. A possible explanation is the posterior leakage of the RhBMP-2 from right side annulectomy. During the final procedure, stenosis of the left L4 nerve root wasn't observed though she has also mild left leg pain. On the other hand, right side L4 nerve stenosis was obvious due to the new bone formation. The tissue was immature bone and it was easily removed from around the nerve root.

Bone morphogenic proteins are very potent osteoinductive agents. Classical definition of osteoinduction is ability to induce de novo bone formation at a nonbony site.[15] If we review this description we would realized that using the potent osteoinductive agents could be unfavorable in some situations of spine surgery. While the use of these agents can significantly increase fusion rates, surgeons should be aware of the risk of heterotopic bone formation proximal to the neural structures with potential for stenosis. Key elements of safe BMPs usage are careful placement of the carrier away from decompressed area and retention within the planned fusion area.[13]

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