observed that 62- to 74-week-old SD rats showed the same histology and PCR results as the 32-week-old rats (data not shown); it was thus believed that there would be no problem in using the 32-week-old model from this study as an "old" model. However, to resolve these issues, it would be desirable to compare the gene expression of anabolic cytokines in IVDs by using human samples of different ages.

There are no reports of a specific study of the TGF-β super family Smad transcription factors in the IVD; however, the involvement of a Smad pathway in articular cartilage differentiation has been reported [17]. Studying the gene expression of intracellular Smad transcription factors in the IVD provides new knowledge for cytokine therapy. Study 1 revealed that the decrease in PGs in aged NP tissues is influenced by decreases in TGF-β2, TGF-β3, and BMP-7, among the TGF-β super family. It has been suggested that TGF-β2 might be involved as a transcription factor R-Smad, with involvement of Smad3 in TGF-β3 and Smad5 in BMP-7. In addition, the key I-Smad in the IVD was not Smad7, which is involved in the inhibition of TGF-β signals, but was Smad6, which is involved in the inhibition of BMP signals; this indicates that this expression is minimally affected by aging.

From the overall NP results, the Smad5 transcription factor that is involved with BMP signals decreased with aging, but there was no change in the expression of Smad6 that is involved with the inhibition of BMP signals; this may indicate that it is likely that the relative inhibition of BMP signals led to the decrease in PG content. This suggests that BMP signals in the TGF-β family are likely to be key factors in IVD degeneration with aging.

Additionally, it has been reported that a TGF-β activated kinase 1 (TAK1), which is activated by TNF-α, and a mitogen-activated protein kinase (MAPK) pathway serve as negative regulators for a Smad pathway [18]. However, according to the results of Study 2, the expression of the R-Smads significantly decreased in the TNF-α-treated NP cells; thus it is proposed that that the decrease in PG synthesis caused by TNF-α was also influenced by cross talk with the TGF-β pathway through this pathway as well as the involvement of the proteolytic enzymes, MMP and ADAM-TS. In assessing the results of Study 1 and Study 2, the effects of aging and treatment with TNF-α produced similar results; although there were differences between tissues and cells; this again indicated that TNF-α might be involved in the aging of IVDs.

The results of this study correlate with the findings in recent reports by Imai et al. [19,20] on the *in vitro* or *in vivo* efficacy of BMP-7 (otherwise known as osteogenic protein-1: OP-1) on IVD cells. Stimulating the replenishment of the decreased PG content in the NP of IVDs that results from aging by treatment with exogenous BMP is believed to be a physiologically effective treatment method [21]. However, there are problems associated with treatment with BMPs, including ossification and an undetermined half-life within an organism. Further results on the efficacy f BMPs are expected in the future, including long-term data.

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Age-Related Effects of Cocultured Rat Nucleus Pulposus Cells and Macrophages on Nitric Oxide Production and Cytokine Imbalance

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Study Design. A study of age-related effects on nitric oxide (NO) and cytokine production in cocultured rat nucleus pulposus (NP) cells and macrophages.

Objective. To evaluate the effects of age on NO and cytokine production in an *in vitro* model of cocultured NP cells and macrophages.

Summary of Background Data. It is well known that the clinical characteristics of lumbar disc herniation differ with age. The relationship between age-related differences in clinical features and immuno-chemical factors, such as NO and inflammatory cytokines, has not been established.

Methods. Male Sprague Dawley rats (n = 45), including 15 animals from 3 groups (3-, 12-, and 32-weeks old), were used. NP cells and exudated peritoneal macrophages were cocultured in serum-free media. NO levels were measured at 2-, 24-, 48-, and 72 hours using the Griess method. After 7 days of culture, the production of cytokines, including tissue inhibitor metalloproteinase-1, interferon-gamma (IFN-gamma), and interleukin-10 (IL-10) were evaluated.

Results. NO levels of coculture increased with age. In the coculture groups, tissue inhibitor metalloproteinase-1 and IFN-gamma level of 3 weeks old were statistically higher than 12 and 32 weeks old. IL-10 level of 3 weeks old was statistically lower than 12 and 32 weeks old.

Conclusion. NO levels of cocultures increased with age that suggests inflammatory reactions increase with age. This study showed an age-related cytokine imbalance, as represented by levels of IFN-gamma and IL-10. Stress and aging are thought to affect the extracellular matrix and change the immunologic response. Younger rat NP cells had higher cell-mediated immunity activity, while the older rat had higher humoral immunity activity. These results demonstrate that age affects the immunologic response attributable to NP cells. Further studies are needed to elucidate the mechanism of this newly observed occurrence and to apply these findings clinically.

Key words: nitric oxide, cytokine imbalance, nucleus pulposus, macrophage, age. **Spine 2008;33:845–849**

Mechanical compressive factors and chemical factors are involved in the appearance of symptoms of lumbar disc herniation. In 1969, Nachemson *et al*[1] reported that pH levels within a herniated lumbar disc, and in its peripheral tissues, decreased and speculated that this phenomenon was influenced by an inflammatory reaction around the nerve root. Subsequently, chemical factors involved in the inflammatory reaction, including glycoprotein,[2] immunoglobulin G,[3] phospholipase A_2,[4] stromelysin,[5] nitric oxide (NO),[6] and prostaglandin E_2[7] have been reported. In lumbar disc herniation, NO is produced, for the most part, by inflammatory cells in the granulation tissue that surrounds the herniated disc materials.[8] An inflammatory reaction has been implicated as the mechanism that is largely responsible for the sciatica found in lumbar disc herniation.[9–13] While the lumbar disc is the largest avascular tissue in the human body, during lumbar disc herniation the nucleus pulposus (NP) leaks into the epidural space, which has an abundant blood flow. Several reports have speculated that the herniated NP is recognized as a foreign matter, inducing inflammation through an autoimmune response.[9,10]

The clinical manifestations of lumbar disc herniation vary with age. Younger patients who are 16 years old or younger present with lumbago (85%), sensory disturbance (10%–21%), and muscle weakness (32%–40%). A higher percentage (64%) of adult patients report sensory disturbance and muscle weakness and are also more likely to report severe sciatica.[14,15] The reasons for the age-related differences in the clinical features of lumbar disc herniation have yet to be elucidated. However, in a histologic analysis of a dog model, Hasegawa *et al*[16] reported that herniated NP fragments elicited less nerve root damage and less inflammatory response in young animals compared with older animals.

With this background in mind, we hypothesized that age-related variations in the clinical symptoms of lumbar disc herniation are influenced by differences in the type of inflammation induced and in the immune response to this inflammation, and that macrophages play an important role in this reaction. The purpose of this study was to investigate age-related effects on NO and cytokine production and differences in immune response in an *in vitro* model using coculture rat NP cells and macrophages in order to shed light on the causes of age-related differences in clinical symptoms of lumbar disc herniation.

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■ Materials and Methods

Male Sprague Dawley rats (n = 45) (Nihon Charles River Co., Kanagawa, Japan), including 15 animals from 3 different age groups (3-, 12-, and 32-weeks old), were used in this study.

Cell Isolation and Culture. Experimental peritonitis was induced by the intraperitoneal injection of 3 mL of 3% thioglycolate (Becton Dickinson, Franklin Lakes, NJ) to 45 rats of each age group. Three days later, each rat was killed while under general anesthesia by diethyl ether (Nacalai Tecsque Inc., Kyoto, Japan) exposure. To isolate macrophages, the peritoneal fluid was aseptically collected and macrophages were isolated by centrifuging at 1000 rpm at 4°C for 5 minutes for each rat. Isolated macrophages were cultured monolayer in Dulbecco's Modified Eagle's Medium (Gibco, Grand Island, NY) containing 10% bovine serum (Sigma Aldrich, St. Louis, MO) before the mono-culture and coculture.

The tail was dissected aseptically to obtain an intervertebral disc. Each disc was cut transversely, and NP was separated from the disc. Obtained NP tissue was digested in 0.025% trypsin ethylene diamine tetraacetic acid (Gibco, Grand Island, NY) for 5 minutes. The digested cells were cultured monolayer for each rats for 24 hours using Mesenchymal Stem Cell Medium (Cambrex, Baltimore, MD) before the monoculture and coculture.

In this study, 3 types of cultures were used for each age group: (1) monoculture of NP cells in monolayer, (2) monoculture of macrophages in monolayer, and (3) coculture of NP cells and macrophages with cell-to-cell contact (Figure 1). In coculture model, the 3×10^4 NP cells and 4×10^5 macrophages which obtained from same rat were seeded in each age group. Six-well culture plate (Becton Dickson, Franklin Lakes, NJ) and culture insert (Becton Dickson) were used for culture. The culture insert consists of a polyethylene terephthalate track-etched membrane with 0.4 μm pores at the bottom, which prevent an exchange of cellular component. Forty-five sets of culture plate and insert were made for each age group, which consisted of 15 sets of each culture type.

After 24 hours, the culture medium was removed and macrophages and NP cells were washed with phosphate-buffered saline (Sigma Aldrich, St. Louis, MO). And then the 3×10^4 NP cells and 4×10^5 macrophages were seeded in each age group, and 15 sets of each group were made as mono-culture models, respectively. In coculture model, macrophages were cultured on the reverse side of the membrane of the insert and NP cells were seeded on the front side of the membrane in Opti-Modified Eagle's medium (Gibco, Grand Island, NY) at 37°C in a humid atmosphere containing 5% CO_2. The medium was not exchanged for 7 days.

Evaluations. NO and cytokine productions were evaluated for all groups.

Measurement of NO Production. The culture media (80 μL) were collected at 2-, 24-, 48-, and 72-hours for NO production analysis. NO levels in the culture media were measured by the Griess method using the colorimetric NO2/NO3Assay Kit-C II Griess Reagent Kit 1(Dojin Chemical Institute, Kumamoto, Japan). The results were statistically processed by the Newman-Keuls method (STATMATE, AVICE, Tokyo, Japan) of 1-way analysis of variance. The level of significance was $P < 0.05$.

Cytokine Production. On day 7 of coculture, the culture media were analyzed for an array of cytokines (Figure 2), including tissue inhibitors metalloproteinase-1 (TIMP-1), interferon-gamma (IFN-gamma), and interleukin-10 (IL-10), using the Cytokine Antibody Array 1.1 for Rat (R&D Systems Co., Minneapolis, MN). For each experimental age group, monocultures of NP cells, mono-cultures of macrophages, and cocultures of both cell types were analyzed and photographed by the Kelmini photographing equipment (Light Capture ATTO Co., Tokyo, Japan) (Figure 2). The images obtained were analyzed by dedicated analysis software (CS Analyzer ATTO Co.,

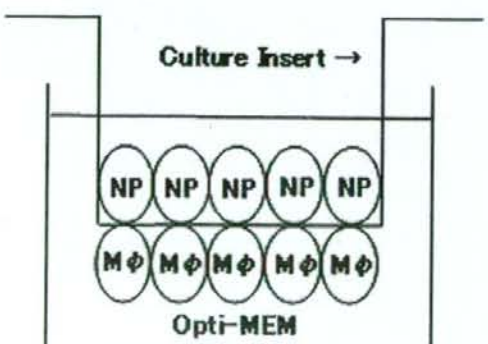
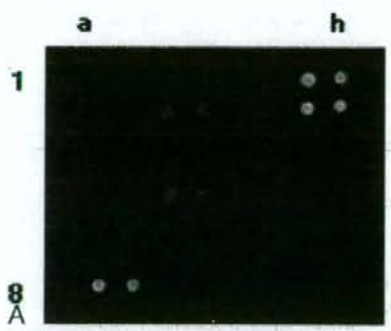


Figure 1. Coculture model using culture insert. NP, nucleus pulposus; MΦ, macrophage; Opti-MEM, Opti-Modified Eagle's medium.



	a	b	c	d	e	f	g	h
1	BLANK	BLANK	Leptin	Leptin	GM-CSF	GM-CSF	Pos	Pos
2	BLANK	BLANK	MCP-1	MCP-1	IFN-γ	IFN-γ	Pos	Pos
3	BLANK	BLANK	MIP-3α	MIP-3α	IL-1α	IL-1α	Neg	Neg
4	BLANK	BLANK	β-NGF	β-NGF	IL-1β	IL-1β	Neg	Neg
5	BLANK	BLANK	TIMP-1	TIMP-1	IL-4	IL-4	CINC-2	CINC-2
6	BLANK	BLANK	TNF-α	TNF-α	IL-6	IL-6	CINC-3	CINC-3
7	BLANK	BLANK	VEGF	VEGF	IL-10	IL-10	CNTF	CNTF
8	Pos	Pos	BLANK	BLANK	LIX	LIX	Fractalkine	Fractalkine

Pos: positive control
Neg: negative control
MCP-1: monocyte chemoattractant protein-1
MIP-3α: macrophage inflammatory protein-3 alpha
β-NGF: beta-nerve growth factor
TIMP-1: tissue inhibitor of metalloproteinase-1
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor
GM-CSF: granulocyte/macrophage-colony stimulating factor
IFN-γ: interferon-gamma
IL-1 α: interleukin-1 alpha
IL-1 β: interleukin-1 beta
IL-4: interleukin-4
IL-10: interleukin-10
LIX: lipopolysaccharide -inducible chemokine
CINC-2: cytokine-induced neutrophil chemoattractant-2
CINC-3: cytokine-induced neutrophil chemoattractant-3
CNTF: ciliary neurotrophic factor

B

Figure 2. Photograph of a representative cytokine array (**A**). Each spot represents the signal from a specific cytokine as shown in (**B**). For each array, the positive control was set at a brightness intensity of 1000 and the other spots were comparatively measured.

Table 1. NO Levels in Monoculture of Nucleus Pulposus Cells Over Time (μmol/L)

	3 wk	12 wk	32 wk
2 h	7.2 ± 1.0	7.5 ± 0.6	7.7 ± 0.6
24 h	8.5 ± 1.2	9.1 ± 0.5	9.4 ± 0.5
48 h	9.6 ± 1.6	10.2 ± 0.7	10.8 ± 1.0
72 h	11.0 ± 1.0	11.6 ± 1.4	11.9 ± 1.6

Tokyo, Japan). For each array, the positive control was set at a brightness intensity of 1000 and the other spots were compared. The data were then processed statistically by the Newman-Keuls method of 1-way analysis of variance. The level of significance was $P < 0.05$.

■ Results

NO Production. In the mono-cultures of rat NP cells, there were no statistically significant differences among the age groups (3-, 12-, and 32-weeks old) at each time in culture (2-, 24-, and 48-hours) (Table 1). Similarly, in the monocultures of rat macrophages, there were no significant differences among the age groups at each time in culture (Table 2).

In the cocultures of rat NP cells and macrophages, there were no significant differences among the age groups after 2-hours of culture. After 24-hours of culture, levels of NO production in the older rat cell cocultures were statistically greater ($P < 0.001$) than in those found in younger rat cell cultures (Table 3).

Cytokine Production. In the mono-culture of NP cells group, the TIMP-1 level of 3 weeks old group was statistically greater when compared with 12 and 32 weeks old groups ($P < 0.001$). Concerning the IFN-gamma levels and the IL-10 levels, there were no statistical differences among the each age group (Table 4).

In the mono-culture of macrophages group, the TIMP-1 level of 3 weeks old group was statistically greater when compared with 12 and 32 weeks old groups ($P < 0.001$). Concerning the IFN-gamma levels and the IL-10 levels, there were no statistical differences among the each age group (Table 5).

In the coculture of NP cells and macrophages groups, the TIMP-1 level of 3 weeks old group was statistically greater when compared with 12 and 32 weeks old groups ($P < 0.001$). There was no statistical difference between 12 and 32 weeks of age. The IFN-gamma level of 3 weeks old group was statistically greater than 12 weeks and 32 weeks old groups ($P < 0.001$). There was no statistical difference between 12 and 32 weeks of age. The IL-10 level of 3 weeks old group was statistically smaller than 12 weeks and 32 weeks old groups ($P < 0.001$). There was no statistical difference between 12 and 32 weeks of age (Table 6).

Table 2. NO Levels in Monoculture of Macrophages Over Time (μmol/L)

	3 wk	12 wk	32 wk
2 h	8.0 ± 0.5	8.0 ± 0.2	8.0 ± 0.1
24 h	8.1 ± 1.4	8.2 ± 1.0	8.8 ± 1.2
48 h	9.1 ± 0.6	8.8 ± 1.0	9.3 ± 1.0
72 h	10.6 ± 0.9	10.3 ± 0.8	10.5 ± 1.2

Table 3. NO Levels in Coculture of Nucleus Pulposus Cells and Macrophages Over Time (μmol/L)

	3 wk	12 wk	32 wk
2 h	8.1 ± 0.9	8.2 ± 0.7	8.3 ± 0.7
24 h	9.0 ± 1.0*	10.1 ± 0.5*	12.1 ± 1.1*
48 h	11.1 ± 1.1*	13.1 ± 0.9*	14.2 ± 0.7*
72 h	13.6 ± 0.7*	16.6 ± 0.6*	18.3 ± 0.7*

*$P < 0.001$.

■ Discussion

When a study that addresses age-related differences in the clinical symptoms of lumbar disc herniation is conducted in an animal model, the rationale for the selected age range of the experimental animal should be discussed. However, there are no reports on animal aging clearly comparing rats with humans. Generally, the age of an animal can be expressed in terms of sexual maturity. In the rat, the age of sexual maturity is believed to be between 9 and 14 weeks.[17] In this study, rats aged 3-, 12-, and 32- weeks old were used. This would seem to be a reasonable model relating to sexual maturity in the human.

NO is considered to be an inflammatory mediator[18] that has been reported to be a cause of radiculitis due to lumbar disc herniation.[8] In this study, age-related chemical changes related to the clinical symptoms of lumbar disc herniation were analyzed by comparing NO production levels among the coculture of NP cells and macrophages derived from rats of different ages.

Macrophages are antigen-presenting cells that transmit signals to helper T (Th) cells, which control specific reactions of the immune system.[19] Therefore, macrophages play an important role in the production of cytokines.[20] In an *in vivo* dog model of lumbar disc herniation, Hasegawa *et al*[16] reported that the appearance rate of inflammatory cells, which were predominantly macrophages, differs with the age of the dog. In other words, the severity of inflammation occurring around the herniated NP differs

Table 4. Cytokine Levels in Monoculture of Nucleus Pulposus Cells (×1000/control)

	3 wk	12 wk	32 wk
TIMP-1*	229.9 ± 13.3†	67.2 ± 10.9†‡	45.5 ± 17.9*‡
IFN-γ§	55.7 ± 27.6	59.6 ± 9.6	50.7 ± 7.4
IL-10¶	41.9 ± 13.6	54.9 ± 7.4	24.6 ± 5.3

*Tissue inhibitor of metalloproteinase-1.
†$P < 0.001$.
‡ns: not statistically significant.
§Interleukin-10.
¶Interferon-gamma.

Table 5. Cytokine Levels in Monoculture of Macrophages (×1000/control)

	3 wk	12 wk	32 wk
TIMP-1*	176.6 ± 21.9†	78.3 ± 17.3†‡	57.5 ± 6.6†‡
IFN-γ§	57.3 ± 23.0	58.0 ± 18.2	52.0 ± 3.1
IL-10¶	45.5 ± 23.9	58.4 ± 21.3	35.4 ± 7.0

*Tissue inhibitor of metalloproteinase-1.
†$P < 0.001$.
‡ns: not statistically significant.
§Interferon-gamma.
¶Interleukin-10.

with age. This condition is assumed to mainly affect the immune response of cytokines accompanying the inflammation. In this study, we considered macrophages to be specifically inflammatory cells and developed a method to coculture NP cells and macrophages to investigate the inflammation and immune response induced by NP cells.

The coculture model used in this study was based on that developed by Yamamoto *et al*,[21] in which NP and stromal cells were cocultured using cell culture inserts. This method was proposed as a useful coculture model that examines the interaction between cells through the culture media. Using this technique, a coculture model of NP cells and macrophages was developed for these studies.

In 1996, the role of NO as an inflammatory factor in lumbar disc herniation was proposed by Kang *et al*,[22] who reported that NO production was found in the biochemical examination of disc herniation tissue extracted from humans. Brisby *et al*[18] reported that NO is produced from NP tissue that was exposed to the epidural space and NO causes neuropathic pain. Kado[23] verified that the exposure of nerve tissues to NP tissues causes neuropathic pain when he found c-fos positive cells at the level of the spinal cord exposed to NP tissue. In this study, the NO levels of the coculture of rat NP cells and macrophages increased with the age of the NP cells. These results suggest that inflammation, and therefore pain, increases with age. Clinically, older patients experience more severe pain of the lower extremities and more perceptual disorder than younger patients.[14,15] Our findings suggest that the level of NO around the nerve tissue in lumbar disc herniation may be a factor in producing age-related differences in clinical symptoms.

Table 6. Cytokine Levels in Coculture of Nucleus Pulposus Cells and Macrophages (×1000/control)

	3 wk	12 wk	32 wk
TIMP-1*	302.8 ± 17.9†‡	121.5 ± 32.5†	107.1 ± 8.1†‡
IFN-γ§	75.0 ± 8.2	62.4 ± 14.1	41.2 ± 11.8
IL-10¶	45.1 ± 20.6	89.4 ± 30.6	94.3 ± 8.6

*Tissue inhibitor of metalloproteinase-1.
†$P < 0.001$.
‡ns: not statistically significant.
§Interferon-gamma.
¶Interleukin-10.

The levels of NO found in inflammation are related to the regulation of the immune function.[24] Because the differences in inflammation cannot be explained just by the age-related differences in NO levels, the possibility that the immune response differs when the NP is exposed to macrophages also exists. In inflammation, NO is converted to various reactive nitrogen oxides through an oxidation reaction; the electron oxides of NO [NO_2 or peroxynitrate (ONOO-)] may induce apoptosis.[25,26] Therefore, as NO production levels increases with age, apoptosis of NP may be induced, changing the biochemical and immunologic nature of NP cells. Future studies should address this possibility.

In this study, the TIMP-1 levels in all the 3-weeks old rat cell cultures, both mono-cultures and coculture, were higher than in the older age groups. TIMP-1 has been shown to be an inhibitor of matrix metalloproteinases which destroy the extracellular matrix.[27] In addition, TIMP-1 is an activator of cell proliferation.[28] These results suggest that a high TIMP-1 levels found in the coculture model with 3-weeks old rat cells reflect a strong self defense reaction against invasive factors by inhibiting extracellular matrix destruction and increasing cell proliferation.

In 1986, Mosmann *et al*[29] proposed that Th cells can be classified into 2 types of cells, according to the cytokines produced: Type 1 Th (Th1) cells, which include IL-2 cells that activate cellular immunity and secrete IFN-gamma, and Type 2 Th (Th2) cells that produce IL-4,5, and 10, and activate humoral immunity. It has been suggested that the Th1 and Th2 cells are originally in a state of equilibrium and the various pathologic conditions related to the defense against infection and autoimmunity may cause an unbalance in cytokines. It is known that in the immune system when factors, such as aging and stress are present, the differentiation into Th2 cells increases and Th1 cells are suppressed.[30–32] Sandmand *et al*[33] reported that the cytokine balance in human blood changes from predominately Th1 type to predominately Th2 with age. Examination of the cytokine balance in the results of this study shows that the balance changed with aging from predominately Th1 cells with a high IFN-gamma level to predominately Th2 cells with a high IL-10 level. This suggests that the immune response of the NP cells in the 3-weeks old rat cell coculture model was predominately cellular immunity; at the 12- and 32-weeks age groups (roughly equivalent to an adult human) the model changed to predominately humoral immunity.

We would suggest that our coculture model of NP cells and macrophages reproduces *in vitro* the exposure of the extruded NP cells to macrophages when lumbar disc herniation occurs. The findings from this study indicate that NO is a cause of age-related differences in the clinical symptoms in lumbar disc herniation. Our results indicate that an age-related cytokine imbalance occurs in areas surrounding herniated NP cells. We think inflammation and increased immunologic response to be non-

specific reaction. The clinical significance of the changes in the immune response with age remains to be examined in future studies.

■ Key Points

- The age-related effects on nitric oxide (NO) and cytokine production were studied in an *in vitro* model of cocultured rat nucleus pulposus (NP) cells and macrophages.
- The NO levels of coculture increased with age.
- Younger rat NP cells had higher cell-mediated immunity activity, while the older rat NP cells had higher humoral immunity activity, demonstrating an age-related cytokine imbalance.

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2度の前方アプローチによる手術を要した腰椎感染症の2例

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化膿性脊椎炎に代表される脊椎感染症は基本的には保存療法が原則とされているが，骨破壊や膿瘍形成などの難治例では手術療法の適応[1)]と考えられる．手術治療は，病巣の広範囲廓清を必要とするため前方進入により排膿，椎体病巣郭清および前方固定術が原則であり，胸腰椎部では胸腔や腹腔に感染が及ばないように胸膜外進入法や腹膜外進入法を用いるのが基本である．しかし，初回手術で治癒しないまたは再発をきたした場合，前方からの広範囲廓清を必要としても，術後癒着のため，2度の同一アプローチは困難である．今回われわれは，初回前方手術により感染症が治癒せず，前方再手術が必要となった難治性脊椎感染症の2例，結核性脊椎炎およびMRSA脊椎炎の治療経験について報告する．

症　　例

症例1：72歳女性．特に誘引なく発熱を伴う腰痛にて関連病院を受診．MRIにて化膿性脊椎炎の診断を受け広域抗生剤治療を3ヵ月施行され症状改善．それから約5ヵ月後に腰痛が出現し，保存療法で反応が乏しいため手術目的に同院入院となる．既往歴として左肩関節結核と，慢性甲状腺炎を罹患していた．理学所見としては腰痛のみで，明らかな神経症状はみられなかった．初回手術では，右下側臥位にて左側腹膜外進入による前方からの病巣廓清およびL3-4間で腸骨を用いた骨移植を行い，病巣の組織培養検査から結核性脊椎炎と診断した．初回術後は，硬性コルセット装着し，INH，EB，REF，PZAを用いた4剤併用抗結核治療を行った．CRPは初回手術後緩やかに低下し術後6ヵ月時，CRPは1以下まで低下したが，腰痛は継続していた．

初回術後，6ヵ月時のMRIでは，L3/4のAxial，T2強調画像で，左腸腰筋に膿瘍形成が認められた（図1中矢印）．前方よりの広範囲病巣廓清が必要と考えられ，外科Drの協力をもとに，経腹的アプローチにて病巣廓清およびドレナージ，再度腸骨を用いた骨移植を施行．さらに不安定性強化のため，前方手術後33日後にL2-5の後方固定術を行った．

2回目術後7年経過時，骨癒合は得られており（図2），局所炎症は沈静化，腰痛は改善しており経過良好である．

症例2：67歳男性．交通事故にて受傷．小腸穿孔による腹膜炎（MRSA）にて，他院にて外科治療受ける．2ヵ月後，発熱を伴う腰痛が生じ，MRIにて化膿性脊椎炎の診断．VCM等の抗生剤治療を3ヵ月施

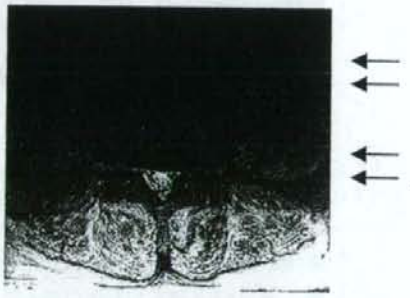

図1　MRI　T2強調画像　L3/4高位

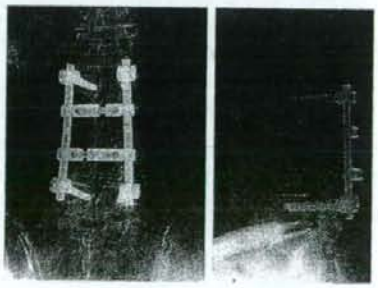

図2　症例1．X線画像

Two cases of pyogenic lumbar spondylitis that needed transabdominal anterior approach for revision surgery：Tatsunori IKEMOTO et al. (Department of Orthopaedic Surgery, Kochi Medical School Kochi University)

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Key words：Pyogenic spondylitis, Transabdominal anterior approach, Posterior instrumentation

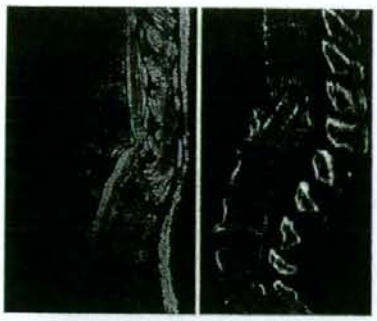

図3　左：MRIT2強調画像　右：CT画像

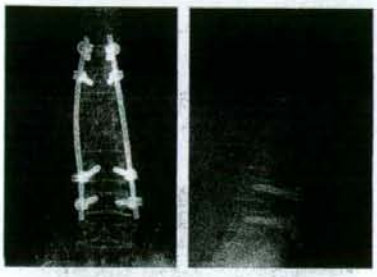

図4　症例2．X線画像

行するも症状改善せず，手術適応にて入院．既往症は特に無く，理学所見としては腰痛のみであった．初回手術では，右下側臥位で左側第12肋骨床を切離し，胸膜外および腹膜外進入による前方からのL1椎体亜全摘，病巣廓清およびLTh12-L1間で自家骨移植を行った．初回術後より硬性コルセット，VCMを中心とした抗生剤治療を行った．術後6ヵ月時，CRPは1以下まで低下したにもかかわらず，術後9ヵ月時腰痛増強し再発と判断された．

初回術後1年時の画像所見にて，MRIおよびCTにて硬膜管への圧迫所見および前方支柱の破壊が認められた（図3）．再度前方よりの広範囲病巣廓清が必要と考えられ，外科Drの協力をもとに，経腹的アプローチにて病巣廓清および自家骨移植を行った．さらに前方手術後23日後にTh10-L4の後方固定術を行った．2回目術後，MRSA抗生剤を6ヵ月施行し，硬性コルセットは6ヵ月着用した．術後2年経過にて骨癒合は完成しており（図4）経過良好である．

考　　察

今回の2症例では，初回手術で胸膜外進入法や腹膜外進入法で再発し，再度前方進入を要する場合でも，外科Drの協力を仰ぐことでサルベージ手術が可能となり，生命予後の改善が期待できることが示された．

また，化膿性脊椎炎への手術療法としては前方からの広範囲病巣郭清術は基本的治療法として確立されているが，後方固定術の意義については未だ統一見解は得られていない[2]．しかし今回の症例では，2例とも初回，2回目術後とも術後療法は同一にも関わらず，2回目は後方固定術を併用することで，治癒することができた．また最近では，前方郭清術と後方固定術の併用から良好な成績の報告も散見されている[1][3]．これらの報告から鑑みても，難治性感染症（結核菌，MRSA）については，初回手術より前方固定＋後方固定を併用する方が推奨すべき治療法であると推察される．

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