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別紙１

厚生労働科学研究費補助金

障害者対策総合研究事業

移植治療後の慢性期完全脊髄損傷患者のリハビリテーションと脳機能再構成および脊髄再生との関連性についての評価法の開発

平成24年度　総括研究報告書

研究代表者　岩月　幸一

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別紙２

研究報告書目次

別紙３

厚生労働科学研究費補助金（障害者対策総合研究事業）
（総括）研究報告書

移植治療後の慢性期完全脊髄損傷患者のリハビリテーションと脳機能に再構成および脊髄再生との関連性についての評価法の開発に関する研究

研究代表者 岩月　幸一　大阪大学大学院　医学系研究科　講師

[研究要旨]
脊髄損傷に対する有効な神経再生療法は未だなく、残存機能の強化リハビリテーションが現在の唯一の治療法である。当グループは損傷後半年以上経過した慢性期完全脊髄損傷患者に対して自家嗅粘膜移植を行い、一定の機能回復を見た。しかし慢性期では下肢筋肉の委縮による神経栄養因子の枯渇から脊髄前角細胞の変性・下位運動神経の不全が起こり、脊髄(上位)神経軸索再生のみでは十分な機能回復は得られないことが示唆される。また効果的なリハビリテーションプログラム開発には、脊髄の組織的再生や脳の神経活動の機能的回復を継時的に評価する必要がある。本研究では、①術前にもリハビリテーションを行い、筋肉由来神経栄養因子の産生と下位運動神経の維持を図る、②自家嗅粘膜移植による脊髄神経軸索の再生、③術後のバイオフィードバックを用いた随意的筋放電の誘発、④長下肢装具およびロボットスーツHAL装着による積極的歩行訓練、の一連のプログラムにより、効率的機能再建を目標とする。さらにDTI(Diffusion Tensor Imaging)による損傷脊髄移植部位の組織的再生の可視化、および脳fMRIによる脳神経活動の再構築により機能回復プロセスの客観的指標の開発を目指す。

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A. 研究目的

脊髄損傷に対する有効な神経再生療法は未だなく、完全脊髄損傷患者においては残存機能の強化リハビリテーションが唯一の治療法である。当グループは損傷後半年以上経過した慢性期完全脊髄損傷患者に対して自家嗅粘膜移植を行い、一定の機能回復を見ているが、慢性期では下肢筋肉の委縮による神経栄養因子の枯渇から脊髄前角細胞の変性・下位運動神経の不全が起こり、脊髄(上位)神経軸索再生のみでは十分な機能回復は得られないことが示唆される。また効果的なリハビリテーションプログラム開発には、脊髄の組織的再生や脳の神経活動の機能的回復を継時的に評価する必要がある。

本申請では慢性期完全脊損患者に術前・術後に積極的リハビリテーションを導入したうえで嗅粘膜移植を行い、より効率的な下肢機能回復を目指すことを目的とする。

B. 研究方法

本研究では機能保存的リハビリテーション・脊髄神経再生・脳神経機能の変化の観点から、下記６つの工程を設ける。

①術前に廃用下肢筋のリハビリテーションにより、筋肉由来神経栄養因子の産生と下位運動神経の維持

を図る。②自家嗅粘膜移植による脊髄神経軸索の再生。③術後のバイオフィードバックを用いた随意的筋放電の誘発。　④長下肢装具装着による積極的歩行訓練。さらに、これら機能回復のプロセスの客観的指標として、下肢運動指標に加え、新たに ⑤DTI(Diffusion Tensor Imaging)で損傷脊髄移植部位の組織的再生を可視化する。⑥脳 fMRI で脳神経活動の再構築を解明する。

(倫理面への配慮)

本研究は、【ヘルシンキ宣言】【臨床研究に関する倫理指針】ならびに本臨床研究実施計画書および同意説明文書を尊守して実施している。

① 同意説明と同意所得

研究責任医師等は治療に先立ち、未来医療臨床研究審査・評価委員会の承認を得た同意説明文書を用いて文書による同意を得る。同意取得のため研究責任医師等は、治療への参加に関し、被験者に強制するなど不当な影響を及ぼすことのないよう留意する。

本臨床研究への参加は被験者本人の自由意思による同意を、同意書に署名または記名・捺印し、日付を自ら記入することにより取得する。同意取得後、同意書の写し及び同意説明文書を同意者本人に交付する。

② 同意の撤回

一旦書面による同意を行った被験者であっても、嗅粘膜移植術実施前であればいつでも撤回できる。

③ 臨床研究内容の開示

同意説明を行った患者、または被験者に本臨床研究実施計画書の開示を要求されれば、それに応じるものとする。

④ 同意書および同意説明文書の改訂

研究責任医師等は、研究に継続して参加するか否かについて被験者の意思に影響を与える可能性のある情報や、被験者の同意に関連しうる新たな情報を入手した場合には、当該情報を直ちに口頭で被験者に伝える。また、情報提供した旨を診療録に記録し、被験者が研究に継続して参加するか否かを確認する。被験者が未成年の場合は、同時に法定代理人に対してもこれを行う。

C. 研究結果

嗅粘膜移植においては脊髄損傷後、骨損傷に対する治療やリハビリテーションを行ったにもかかわらず、6か月後に完全対麻痺を呈する胸髄損傷患者を対象とした。採取可能な嗅粘膜の量が限られているため、損傷部位の長さは3cm 以下である。術後早期から連日リハビリテーションを行うと、4例中2例において6カ月後より運動機能の改善がみられ、うち1例では装具を用いた立位保持や歩行器を用いた歩行が可能となった。4名いずれの患者においても「両手を離しての動作が楽になった」、「エレベーターのボタンを押すのが楽になった」、「長時間の坐位での作業が可能となった」など、日常生活上何らかの運動機能改善が自覚された。ASIA Scoringのうち、運動スコアは、１名(case 3)では24週以後50から52に改善し、他1名(case 4)では24週に50から52に、48週で54に改善した。この２症例で随意性の下肢筋収縮による筋電図の発現を認め、さらにCase 4では、経頭蓋磁気刺激によるmotor evoked potentialの下肢からの導出に成功し、慢性期の完全脊髄損傷において、電気生理学的に神経軸索の再建を世界で始めて証明し得た。感覚および膀胱直腸障害においては変化を認めなかった。

D. 考察

移植後のリハビリテーションは、完全両下肢運動麻痺慢性期患者の歩行という、これまでにないリハビリテーションを実施しなくてはならなかった。中枢神経の神経ネットワークの再構築のため、長期間にわたるハードなものとなった。HAL を導入し、検出される生体信号が徐々に下位に延びてくるのにあわせてプログラムを変更することで、科学的リハビリが可能となった。またトレッドミルと免荷装置を併用することで、安全且つ省力的なリハビリが可能となった。さらに初期の段階から患者に歩行を体感させることが可能となり、これは長く単調になりがちなリハビリテーションに対する患者のモチベーションの維持に、大きく貢献したものと思われた。

E. 結論

慢性期完全脊髄損傷患者に対し、嗅粘膜移植と積極的リハビリテーションを行い、一定の機能回復を導き、かつ下肢筋電図の導出に初めて成功した。このことは、損傷後数年以上を経た慢性期脊髄損傷患者の機能再建とQOLの向上に新たな道を拓くものである。

F. 健康危険情報

実施した4例において、これまで当研究と関連があると判断される感染症、悪性新生物の発生を認めていない。有害事象として嗅覚低下や、頭痛および脊損領域の痛みが出現した症例もあるが、

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대한척추외과학회 회장 이 환 모

Intradural Extramedullary Spinal Ependymoma: A Case Report of Malignant Transformation Occurring

Running Title: Intradural extramedullary spinal anaplastic ependymoma

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Abstract

Intradural extramedullary spinal ependymomas are extremely rare. Herein, we describe a lesion-type spinal ependymoma that followed a malignant course, and discuss its clinical presentation, etiopathogenesis, and treatment. We present a patient who was diagnosed with an intradural extramedullary spinal tumor at T4-T6. The patient underwent gross total resection of the tumor without damage to the spinal cord. Histological examination, classified the lesion as a World Health Organization (WHO)-grade 2 ependymoma. One and a half years later, magnetic resonance imaging detected a recurring tumor at T4-T5. The tumor was removed and classified as a WHO-grade 3 anaplastic ependymoma. The patient was started on a course of regional spinal cord radiotherapy. The patient achieved tumoral control and clinical stabilization after the recurrence. We must consider the differential diagnosis of intradural extramedullary spinal tumors. The best treatment for this lesion is gross total resection and adjunctive radiotherapy is necessary in cases of malignant-change.

Keywords: Ependymoma; Intradural Extramedullary Spinal Cord Neoplasms; Spinal Cord Tumor

Introduction

Spinal ependymomas are the most common intramedullary tumors and occur predominantly in adults. Other than those located at the terminal filum or conus medullaris, intradural extramedullary ependymomas are extremely rare [1]. Ependymomas arising outside the lesion of the conus medullaris, cauda equina, and terminal filum, or developing from ectopic ependymal cells are highly unusual [2,3].

Although these tumors are most often benign, a few may follow a more malignant course. Anaplastic transformation and cerebrospinal fluid dissemination rarely occur [2,3].

We describe a rare case and malignant course of intramedullary ependymoma and discuss its clinical presentation, etiopathogenesis, and treatment.

Case Report

A 23-year-old woman was admitted to our institution on January 2009. Her symptoms included a backache around her right shoulder, parasthesia in the left lower limb, pain in the left abdominal region, and difficulty walking smoothly (as a result of the backache and pain). The patient had first noticed the backache 4 months before admission, and her neurological status progressively worsened.

Neurological examination revealed slightly motor weakness of left lower limb. She had sensory disturbances of above. Examinations were negative for the Romberg sign, with bilateral Babinski's sign. Deep tendon reflexes were nearly symmetrical in the lower extremities. Urinary function, rectal tone, and perianal sensation were normal.

Cranial computed tomography (CT), and abdominal, chest X-ray were within normal range, magnetic resonance imaging (MRI) of the thoracic spine (Fig.1-A,B) showed a posterolateral intradural extramedullary mass compressing the spinal cord at the T4-T6 levels. The mass was of low intensity in medullary tissue for T1 imaging and of slightly high intensity in the T2 sequence, with homogeneous enhancement after gadolinium injection. Its limits were well defined, occupying 60% of the posterior and left spinal canal without bone destruction or foramen invasion, suggesting schwannoma or meningioma as the first option. No other lesions were present along the neuroaxis,

including the posterior fossa.

Because the tumor was present in the left spinal canal, a left hemilaminectomy from T4 to T6 (Fig.2) was performed, uncovering an intradural extramedullary encapsulated mass. We determined that the tumor was not connected to the dura mater or spinal roots, and had not infiltrated the spinal cord. Only mild adhesions to the spinal pia mater were found and were carefully stripped away.

A gross total resection was completed without damage to the medulla, using an ultrasonic surgical aspirator under an operating microscope.

Anatomic-pathologic studies were performed. Immunohistochemical examination (Fig.3-A,B,C) demonstrated strong immunopositivity with anti-glial fibrillary acidic protein, especially in perivascular pseudorosettes, but there was no immunostaining with the epithelial membrane antigen. Neither cystic degeneration nor anaplastic change was present, but the Ki-67 index was 5% to 10%. Histological examination revealed a World Health Organization (WHO)-grade 2 ependymoma with hypercellular nodules that demonstrated a high Ki-67 index.

The patient's neurologic condition improved after surgery and she was discharged from the hospital with mild paresthesia and pain in the left abdominal region. Neither radiotherapy nor chemotherapy was performed. We carried out close follow-up by MRI (Fig.4-A,B).

One and a half years later, the patient's physical and neurological condition had worsened, with increased pain in the left abdominal region. MRI of the thoracic spine (Fig.5-A,B) uncovered a recurring mass at the T4-T5 levels: a posterior intradural extramedullary tumor.

A T4-T6 laminectomy (Fig.6) was performed; the tumor was removed and classified as a WHO-grade3 anaplastic ependymoma (Fig.7-A,B,C). The patient was started on a course of regional spinal cord radiotherapy, which was 50.4 Gy/28 Fr. The symptoms in the left abdominal region decreased. Neither worsening nor deterioration was observed after surgery and radiotherapy treatment, with the patient achieving tumoral control and clinical stabilization with a total follow-up of 17 months after the recurrence.

Discussion

Spinal ependymomas are typically intradural intramedullary tumors, and are often described as benign

cases presented in the literature [5].

This lesion-type tumor is believed to arise from ectopic ependymal cell rests. Some ependymal cells may remain on the inside during neural tube closure [8].

In all cases, these types of ependymomas were encapsulated with only microvascular attachment to the spinal cord, and could be removed completely. However, there was mild adhesion to the spinal pia mater in the present case. After complete resection, we carried out close follow-up because of the potential for recurrence, metastasis, and anaplastic transformation.

Although ependymomas are most often benign [9], there have been 3 previous reports of malignant transformation occurring [1,2,10]. In this case, histological examination of the second operation identified malignant transformation. This malignant transformation may have led to the recurrence. However, second operative views showed that the recurring ependymoma was more strongly adhered to the spinal pia mater than that of the first views. In the first operation, there was slight adhesion between the spinal pia mater and the encapsulated tumor by a tumor membrane that was unconnected to the posterior spinal roots, spinal cord, and spinal pia, and dura mater. This patient underwent gross-total resection of a posterolateral tumor; however, there was an absence of medullary contusion to prevent surgical complication at the adhesion lesion, which was slight. This slight lesion would have retained a few ependymoma tumor cells, and these cells might have contained malignant components. During the close follow- up periods, some of these lesion cells underwent a malignant change, infiltrated the spinal pia mater, and the posterior spinal cord. As a result, these changes led to tumor recurrence. Tumor recurrence would not have occurred after the first operation if a part of the adhesion lesion had not contained ependymoma tumor cells, or if those cells had not undergone malignant change. Therefore, the few ependymoma cells that remained after the first operation might have adhered to the spinal pia mater, undergone anaplastic change, and carried out meningeal infiltration, which means that the possibility of tumor cell remnants remaining in the area cannot be ruled out.

The best treatment for an extramedullary ependymoma is gross total resection, as was carried out in this case; adjunctive radiotherapy is necessary in malignant-change cases. The extent of resection and the presence of meningeal infiltration appear to be very important factors of patient prognosis.

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Figure legends

Fig. 1. Sagittal T1-weighted, gadolinium-enhanced (A), axial T1-weighted, gadolinium-enhanced (B) views of preoperative magnetic resonance imaging (3.0T) displaying the posterolateral intradural extramedullary T4-T6 ependymoma with spinal cord compression displaced ventrally.

Fig. 2. A posterior T4-T6, left hemilaminectomy allowed intradural exploration and removal of the intradural extramedullary mass (star). A reasonable dissecting plane was discerned against the spinal cord, and the tumor was extramedullary with partial adhesion to the posterior spinal cord; however, there was no adhesion to either posterior nerve roots of the T4 (arrow). The tumor was excised in gross total fashion using standard microsurgical techniques.

Fig. 3. (A). The histological features of the ependymoma were observed; perivascular pseudorosettes (arrow) were identified (H&E, original magnification ×200). (B) GFAP immunoreactivity was observed predominantly around tumor vessels (arrow) (GFAP immunostain ×200). (C) The tumor exhibited slightly high proliferative activity (5% to 10%) (Ki-67immunostain, ×100).

Fig. 4. Sagittal T1-weighted, gadolinium-enhanced (A) and axial T1-weighted, gadolinium-enhanced (B) views of post 1st operative magnetic resonance images (3.0T), which displayed no tumor recurrence.

Fig. 5. Sagittal T1-weighted, gadolinium-enhanced (A) and axial T1-weighted, gadolinium-enhanced (B) views of recurrence magnetic resonance images (3.0T) displaying the posterior intradural extramedullary T5-T6 anaplastic ependymoma.

Fig. 6. A posterior T4-T6 total hemilaminectomy was performed and the intradural extramedullary tumor was removed. The tumor had adhered more strongly to the posterior spinal cord than before. However, as before, the tumor had not adhered (arrow) to the posterior nerve roots.

Fig. 7. (A) White arrows indicate densely cellular glial neoplasms with abundant perivascular

pseudorosettes characteristic of an ependymoma (H&E, ×200). (B) GFAP immunoreactivity was observed predominantly around perivascular pseudorosettes (arrow) (GFAP immunostain, ×100). (C) The tumor exhibited significantly high proliferative activity (10% to 15%) (Ki-67 immunostain, ×100).

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Entrapment of the Fifth Lumbar Spinal Nerve by Advanced Osteophytic Changes of the Lumbosacral Zygapophyseal Joint: A Case Report

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A 54-year-old female patient had a 6-year history of backache and left sciatica. Five years earlier, she had undergone surgery in another hospital for left L4-5 disc herniation. Computed tomography revealed the ossified wall that enclosed the left L5 nerve root. There were also osteophytic changes in the left L5-S zygapophyseal joint. These osteophytes developed rostrally, along the left L5 nerve root, through the intervertebral foramina. We performed decompression surgery for the left L5 nerve root, and surgery resulted in symptomatic relief. We experienced a rare clinical presentation of osteophytic formation, with a specific configuration in relation to the nerve root. Surgeons should be aware of entrapment of the lumbar spinal nerve by advanced osteophytic changes occurring in the zygapophyseal joint after lumbar surgery.

Key Words: Osteophyte, Entrapment, Nerve root, Zygapophyseal joint

Introduction

Advanced degenerative changes in the zygapophyseal joints are of essential clinical interest, because the intervertebral foramina obstructed by these processes may cause severe neurological symptoms. This study is a case report demonstrating a rare clinical presentation of osteophytic formation, with a specific configuration in relation to the nerve root.

Case Report

1. History

A 54-year-old female patient had a 6-year history of backache and left sciatica. Five years earlier, she had undergone surgery in another hospital for L4-5 disc herniation. Although her left sciatica subsided, she experienced gradual deterioration of symptoms, including pain, numbness, and weakness in the left leg.

2. Examinations

On referral to our hospital, the patient's neurological examination showed left L5 radiculopathy. The strengths of dorsiflexion were weak at the ankle and great toe. Light touch sensation was decreased over the dorsum of the left foot and pain was present. The left patellar reflex was decreased, but the Babinski sign was absent. Routine laboratory tests were normal and the patient was not diabetic. On magnetic resonance imaging, there was slight L4-5 disc bulging, but no canal stenosis. Computed tomography (CT) revealed that ossified wall enclosed the left L5 nerve root at the lateral recess (Fig. 1A, B). Sagittal and coronal views also showed ossified wall medially located from the left L5 pedicle (Fig. 1C, D). There were also osteophytic changes

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in the left L5-S zygapophyseal joint. Left L4-5 partial laminectomy and left L4-5 partial facetectomy had been performed at previous hospital. Osteophytes originating from the left L5-S zygapophyseal joint developed rostrally, along the left L5 nerve root (Fig. 1).

3. Operation and postoperative course

The imaging findings could explain the left L5 radiculopathy. It is suggested that abnormal ossification of the left L5 lateral recess derived from the osteophytes in the left L5-S zygapophyseal joint. Left L4-5 unilateral laminectomy and partial facetectomy had been performed and the shoulder of the left L5 nerve root was confirmed. The distal segment of the left L5 nerve root was embedded with abnormal ossified formation that corresponded on CT to the ossified wall at the left lateral recess of L5. We drilled this abnormal ossification to expose the left L5 nerve root (Fig. 2A). This ossification continued to the superior left L5 articular process and the distal part of the intervertebral foramina. We carefully decompressed the nerve root from the left lateral recess to the intervertebral foramina (Fig. 2B). The fat tissue in the epiradicular sheath disappeared through the intervertebral foramina. Unfortunately, we could not perform histological examination of these ossified tissues. The lateral half of the left L4-5 joint was preserved. Postoperative CT showed removal of the ossified lesion. After surgery, the patient's neurological function improved, and pain in her left leg subsided. Postoperative external fixation continued for three months.

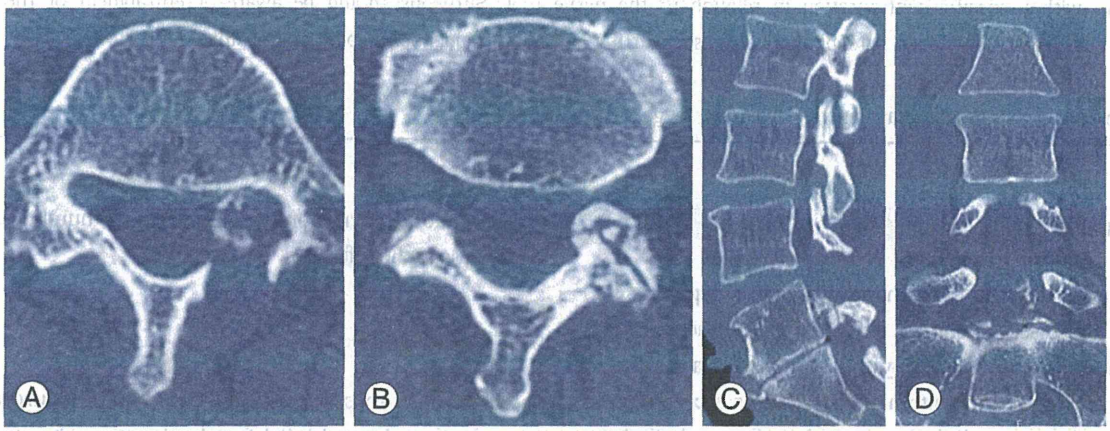

Fig. 1. **(A)** Axial view of the L5 showed the left L5 nerve root encircled by osteophytes. **(B)** Advanced osteophytic changes in the left L5/S zygapophyseal joint. **(C, D)** Sagittal and coronal views showed that osteophytes developed along the left L5 nerve root.

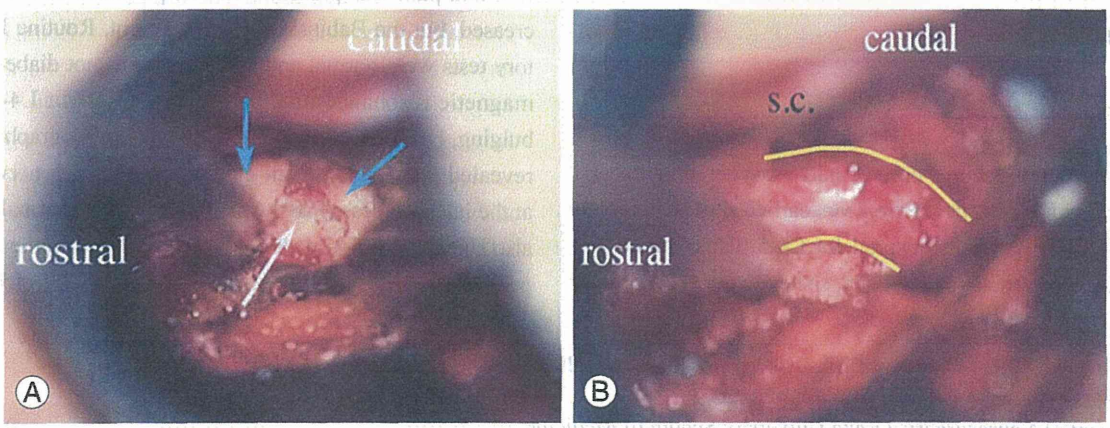

Fig. 2. **(A)** Operative view shows the left L5 nerve root entrapped by the ossified tissue, instead of the fat tissue in the periradicular sheath. Blue arrows indicate the ossified tissue surrounding the left L5 nerve root. White arrow indicates the left L5 nerve root. **(B)** The ossified tissue was removed from the nerve root. The yellow solid line indicates the boundary of the nerve root. S.C.: Spinal cord.

Discussion

This study is a case report demonstrating a rare clinical presentation of osteophytic formation, with a specific configuration in relation to the nerve root. These advanced osteophytic changes in the lumbosacral zygapophyseal joint entrapped the L5 nerve root at the intervertebral foramen. Thus, the lumbar nerve root was compressed and sealed by the ossified tissue. In this case, the fat tissue of the epiradicular sheath disappeared after neurosurgery. The ossification of a lumbar nerve root is extremely rare, though a previous case has been reported in a child, in whom calcified tissue encased the nerve root [1].

The entrapment of lumbar nerve root can occur at three locations: the lateral recess, the intervertebral foramen and extraforamina [2-4]. Decrease in the height of the intervertebral disc, osteoarthrotic changes in the facet joints, cephalad subluxation of the superior articular process and either deflection of the ligamentum flavum or protrusion of the annulus fibrosus may constrict the intervertebral foramen sufficiently to cause entrapment of the spinal nerve root [5]. Moreover, the transforaminal ligaments [6], psuedomeningocele [7], sinovitis [8] and extraforaminal osteophytes [9] can also entrap the spinal nerve root.

Osteophytic formation in the vertebral body is a well documented phenomenon associated with degeneration and altered mechanics of the spine, both of which have been considered to be the result of aging, a physiologic response to load bearing, or intrinsic spinal disease, as etiologic factors. Osteophytes form as a specific tissue reaction to stresses and strains [10].

This patient had undergone surgery for L4-5 disc herniation in another hospital. Thus, the left L4-5 joint had already been more or less injured, before visiting our hospital. Therefore, stresses and strains on adjacent intervertebral joints had been generated after the first operation. Moreover, there were narrow lumbosacral intervertebral distances, whereas the height of L4-5 was preserved. Following the load bearing to the left L5-S zygapophyseal joint after surgery, osteophytic formation had developed.

We experienced a rare clinical presentation of osteophytic formation, with a specific configuration in relation to the nerve root. Surgeons should be aware of entrapment of the lumbar spinal nerve by advanced osteophytic changes in the zygapophyseal joint after lumbar surgery.

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