

# Spinal cord compression by epidural metastases

## Fibrosarcoma experiments in rats

Shohei Manabe, Tohgo Ohno, Hiromitsu Tanaka and Pyoyun Park

Morphologic changes were studied in 43 rats that were paralyzed by an epidural fibrosarcoma inoculated through the spinous process. By this technique, of 29 rats examined radiographically, the tumor destroyed vertebral bone in 22. Changes of the cord in the early stage of paralysis were specially analyzed by Marchi's stain and microangiograms. In compromised cord segments in the early stage, extravasation of contrast medium was observed in the gray matter and the dorsal funiculus; and in the dorsal funiculus just proximal or distal to the compressed portion, hemorrhagic areas were present. Ascending degenerated fibers in the dorsal funiculus, which were derived from the degenerated posterior nerve root or the degeneration of the dorsal funiculus in the compressed segments, were characteristically detected in rats in the early stages. In the advanced stages a transverse cord lesion was observed at the involved level. Based on the present analyses, to prevent more advanced damage to the spinal cord, the tumor should be removed at an early stage that clinically coincides with the period when radicular signs appear.

In spite of many clinical reports on cord compression caused by metastatic epidural tumors, only a few systematic analyses of cord changes caused by the tumor have been performed by experimental or clinocopathologic research (Baron et al. 1959, Boland et al. 1982, Ikeda et al. 1980, Ushio et al. 1977a, 1977b). Little is known of the changes in the fasciculus of the cord, which degenerates in the early stage of the compression by metastatic tumor. We have studied epidural metastases in rats in order to analyze how the spinal cord is compromised in the early stage of the compression and the timetable for cord damage.

### Materials and methods

A cell suspension, containing  $5 \times 10^5$  tumor cells per 0.1 mL in TC-Medium 199, from a serially subcutaneously transplanted fibrosarcoma in-

duced by methylcholanthrene in our laboratory in a Lewis rat was inoculated into the spinous process of rats at the following levels: T7 in 15 rats, T11 in 16 rats, and L2 in 12 rats.

After the inoculation, the rats were checked daily for neurologic symptoms. Paralysis of the hind limbs was graded according to the following modified scale (stage) (Ikeda et al. 1980): Stage 0 = normal; Stage 1 = weak, but able to walk; Stage 2 = attempts to walk; Stage 3 = only moves hind limbs when pricked with a pin; Stage 4 = paraplegia.

The rats were killed at various stages of paralysis (Table 1). The spinal cord was removed carefully under the microscope, followed by histologic and vascular observations.

The spinal cord was classified depending on the site of compression:

Type 1. Anterior compression with or without anterolateral involvement.

Type 2. Posterior compression with or without posterolateral involvement.

Type 3. Lateral compression.

Type 4. Cufflike encirclement of the cord by the tumor.

The morphologic and vascular changes were analyzed according to the stage of paralysis.

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Department of Orthopedics, Teikyo University School of Medicine, Tokyo, Japan

Correspondence: Dr. Shohei Manabe, Department of Orthopedics, Teikyo University School of Medicine, 11-1, Kaga, 2 Chome, Itabashi-Ku, Tokyo 173, Japan

Table 1. Paralysis stages and the time of killing of the animals

Stage	Number of rats	Time (days)
1	2	14
2	4	15
3	6	17
4	31	20

Marchi's investigation was performed on 25 spinal cords. Each cord was fixed and stained in Marchi's solution, after which serial transverse sections of the cord were analyzed. Nine other cords were stained with hematoxylin-eosin and luxol fast blue. Marchi's investigation: The product from degenerated myelin combines with osmium oxide, resulting in black granules. This reaction is observed in secondary degeneration of myelinated nerve fibers within 3 months after the damage of nerve cells and/or nerve fibers in the spinal cord.

Before death, the 9 remaining rats paralyzed in various stages were perfused with Indian ink. Transverse serial sections and longitudinal transverse serial sections of the perfused cord were prepared for microscopic histologic observation of spinal-cord blood vessels.

Of the 43 rats, 29 rats were examined radiographically after death.

## Results

**Neurologic deficits.** When the rats were killed, they had all developed neurologic deficits; the majority were Stage 4 (Table 2). The average duration from inoculation was 17 days for those in Stages 1 and 2, 18 days for those in Stage 3, and 24 days for the rats in Stage 4. In all the rats, the neurologic symptoms were progressive, and 31 rats that were not killed until Stage 3 became paraplegic and had complete sphincter involvement by the third day after they had reached Stage 3.

Table 2. Paralysis stages and tumor types (see text)

Type	Paralysis stage					Total
	0	1	2	3	4	
1	0	1	1	0	4	6
2	0	1	0	0	5	6
3	0	0	1	4	8	13
4	0	0	2	2	14	18
<b>Total</b>	0	2	4	6	31	43

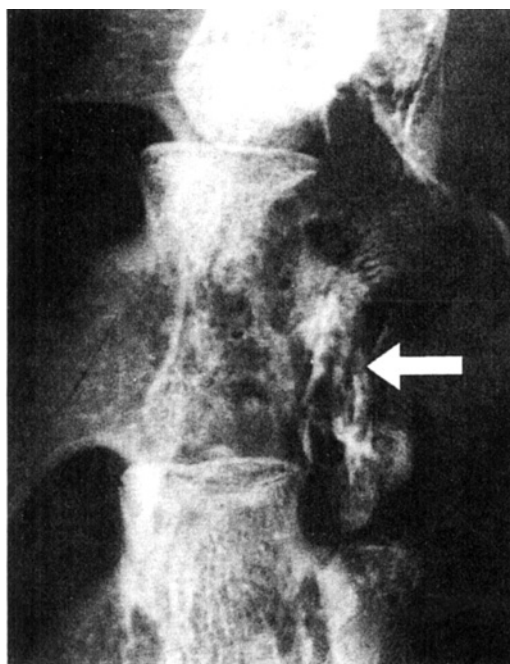


Figure 1. Twenty-three days after inoculation. Osteolytic tumor was observed in a vertebral body and a transverse process (arrow).

**Radiographic and macroscopic findings.** Of the 29 rats that were checked radiographically, an osteolytic tumor of the spine (Figure 1) was observed in 22 rats: the lamina was involved in 10 rats, whereas the lamina and vertebral body were osteolytic in 8 rats, and the vertebral body with a pedicle and a transverse process was destroyed in 4 rats. In 7 rats that had a paravertebral tumor, but no bone destruction, the tumor was revealed to infiltrate the intervertebral foramina into the epidural space.

After the laminectomy, tumors were found to invade epidurally from the destroyed pedicle, lamina, or vertebral body, and appeared to extend over about two spinal segments, involving nerve roots. Among the 43 rats, the tumor formed a cufflike encirclement around the cord in 18 of them, and 13 had a tumor lying laterally to the cord, whereas in the remaining 12 the tumor caused anterior or posterior cord compression.

The cords of 14 rats, or half of those with complete paraplegia, had Type-4 cufflike compression of the cord (Table 2).

**Vascular changes.** In the less advanced compression (Stages 1 and 2), a moderate decrease of



Figure 2. An angiogram of a compressed cord of a rat with paralysis Stage 2. Extravasation of contrast medium in the gray matter.

perforating branches was evident in the compressed portion of the spinal cord, but the major branches of the central and posterior spinal arteries were filled with contrast medium. In all the cords in these stages, microangiographic specimens showed extravasated areas of contrast medium in the gray matter, in which there was a paucity of the capillary network (Figure 2). Small hemorrhagic areas were frequently observed in the dorsal column of the proximal and distal segments adjacent to the compressed portion.

In the more advanced stages, extensive leakage was observed in the compressed portion. The gray matter was almost totally replaced with Indian ink; and dorsal, lateral, and white columns adjacent to the gray matter were also filled with contrast medium. There was no filling of peripheral vessels supplying the white matter, and there was a total lack of normal capillary network in the gray matter. At the level of two or three segments proximal or distal to the compressed portion, leakage was detected in the dorsal, lateral, and sometimes ventral white columns. The capillary network in the gray matter decreased, and there was also a dearth of vessels in the white matter with diffuse narrowing.

The degrees of leakage of contrast medium and the paucity of perforating vessels were proportional to the severity of the paralysis of the rats.

**Histologic findings** Histologic changes of the involved part of the spinal cord were basically proportional to the stage of neurologic symptoms. In Stages 1 and 2 the cord was slightly deformed, had vacuolization, loss of myelin in the white

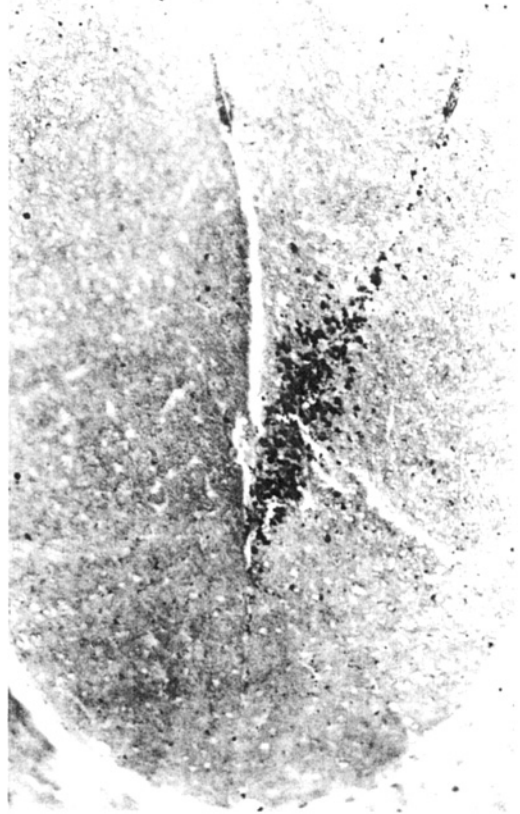


Figure 3. Marchi's granules lined in the dorsal funiculus of the proximal level in a rat with paralysis Stage 2. The 7th cervical segment of the cord involved at the 11th thoracic level.

matter, and the nerve roots were encircled by the tumor. Rats in Stage 2 had relatively large areas of tissue destruction in the dorsal horn and dorsal funiculus, frequently with hemorrhages.

In the more advanced stages, the involved part of the cord was frequently encircled and compressed laterally by the tumor and flattened in an anteroposterior direction. The gray matter was completely destroyed, resulting in gliosis formation. The gliosis was also manifested in the dorsal column and in the lateral white columns adjacent to the gray matter, but rarely in the anterior white column. Hemorrhages were observed in the gray matter and in the dorsal and lateral columns.

In Stage 1, no Marchi's granules were observed in the cord. In Stage 2, there were two types of degeneration in the ascending dorsal funiculus. First, upper segments proximal to the compressed part characteristically had intense Marchi's granules only in fibers of the dorsal funiculus. In the

compressed segments, Marchi's granules were observed mainly in the fibers of the dorsal funiculus in which there were hemorrhagic areas. Another type of degeneration in the upper segments (Figure 3) was shown as a line of Marchi's granules in fibers of the dorsal funiculus that could be traced ipsilaterally and caudally to its origins in the posterior nerve root involved.

In Stages 3 and 4, upper segments far from the compromised level were detected to degenerate in the ascending dorsal, lateral, and ventral funiculi. In the compressed portion, transverse morphologic changes were demonstrated in the cord, and all the fibers in the white matter degenerated. Caudally, far from the involved level, degeneration was observed in fibers of the descending lateral and ventral funiculi; further, a localized large area of necrosis was detected to exist mainly in the anterior portion of the dorsal column (Figure 4). This distinctly localized necrosis, which was detected in cords of 8 rats in Stage 4, was hemorrhagic. The lesions in the dorsal column formed a perpendicular cylinder consisting of anywhere between one to six spinal cord segments from the involved level.

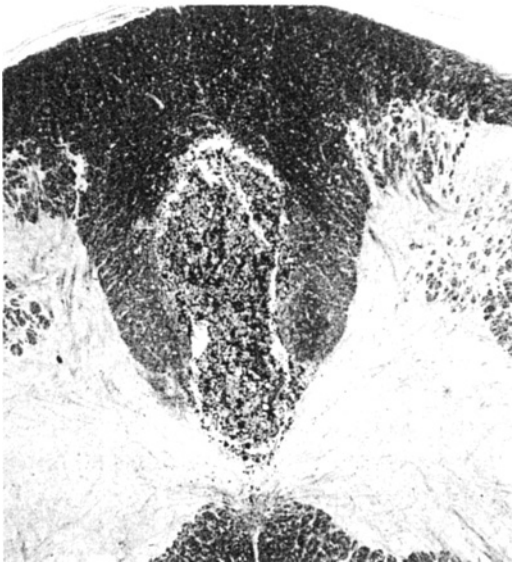


Figure 4. A localized area of necrosis in the dorsal column. The 2nd thoracic segment of the cord involved at the 6th thoracic level in a rat with paralysis Stage 4. Marchi's stain.

## Discussion

Three methods have been reported for the experimental epidural tumor causing cord compression: 1) injection of Walker 256 carcinoma cells into the tail vein (Coman and DeLong 1951), 2) transplantation of Murphy-Sturm lymphoma into the nape of the neck (Rubin 1969), and 3) injecting of Walker 256 carcinoma cells anterior to the thoracic vertebral body (Ushio et al. 1977a, b, Ikeda et al. 1980). Although the tumor inoculated through the tail vein destroyed vertebral bodies and invaded intrathecal space resulting in compression of the cord, Ushio et al. (1977a) pointed out that it was not useful because the level of cord compression was not predictable and was frequently multiple. In the methods of Rubin (1969) and Ushio et al. (1977b), the cord was able to be compressed at the predictable level by intrathecal invasion of a tumor growing in the soft part, but the vertebral bone was not invaded by the tumor, which does not mimic the human metastatic spinal tumor.

In our opinion the model must have bone changes by the infiltration of the transplanted tumor, so it is essential to inoculate tumor cells into the vertebral bone. In our method, bone destruction was observed in three fourths of the rats at the level of tumor inoculation. The tumor invaded from the destroyed pedicle, spinous process, and vertebral body, resulting in epidural infiltration, which caused the same macroscopic feature of the cord as observed in operations of human metastatic spinal tumors. The cord, therefore, was not compromised by the destroyed bone, but by tumor tissue, and extradural infiltration of the tumor also involved nerve roots. The dura was a barrier to intradural tumor invasion.

In addition, from our experiments, we wish to emphasize the following findings:

1) In early stages the microangiograms showed that extravasation of contrast medium occurred not only in the dorsal column and in the gray matter in compromised segments with a paucity of the capillary network, but small hemorrhagic areas were also observed in the dorsal column of the proximal and distal segments adjacent to the compressed portion. These findings are definitely different from those observed following experimental traumatic spinal cord compression (Ducker and Assenmacher 1969, Griffiths 1975).

because the trauma does not produce such early changes of cord compression as the tumor in our experiment.

2) Marchi's stain showed that in the early stages the degenerated fibers of posterior funiculus, which were surprisingly characteristic in the upper segments, could be traced ipsilaterally and caudally to its origins in fibers of the posterior funiculus itself, where there were frequently hemorrhagic areas or deformity by compression in the involved level or in the degenerated ipsilateral posterior nerve root. Investigations, such as Marchi's stain, have neither been reported in human situations nor in experimental metastatic spinal tumors, and early changes in the compromised cord have not been described. In our study, these two morphologic changes were characteristic in the early stages of cord compression.

3) In advanced stages (8 paraplegic rats), in addition to degenerating funiculi derived from compressed segments, distinctly localized necrosis near the involved level formed a perpendicular cylinder mainly in the anterior portion of the posterior column. The cylinder of this degeneration was hemorrhagic and there is a possibility that it could develop into cavitation or pencil-shaped softening, which is frequently observed in the posterior column of human metastatic spinal

tumors (Gruner and Lapresle 1962) and of other involved cords (Fairholm and Turnbull 1970, 1971, Jellinger 1964, Woodard and Freeman 1956).

From these analyses, it appears that after the involvement of nerve roots the spinal cord was compressed by the tumor that invaded epidurally from the destroyed vertebral bone. This process would suggest that our model mimics human spinal metastasis.

Our experiments provide two conclusions concerning the pathologic changes in cord compression from spinal metastases: 1) In the early stage, only the ascending dorsal funiculus was degenerated as a result of compression of nerve roots. In patients, this stage must coincide with the period when radicular symptoms appear. This suggests that if the cord can be decompressed by removal of the tumor in an early stage, more advanced damage to the cord would be prevented. 2) Furthermore, tumor tissue does not always proliferate in one direction toward the cord. By understanding this, we can choose the appropriate approach to decompress the cord; a laminectomy does not always provide satisfactory results. A thorough neurologic and radiographic analysis may greatly improve the surgical treatment of the spinal metastases.

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