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Case Report

Highly Invasive Intracranial Malignant Schwannoma in a Rat

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Abstract: A highly invasive intracranial malignant schwannoma containing several masses was detected in a 28-week-old male Crl:CD(SD) rat. Macroscopically, 3 masses were noted in the cranial cavity; one was present at the bottom of the cranial cavity and involved the trigeminal nerve, and the other two were in the parietal bone. Histologically, each mass consisted of fusiform cells with interlacing fascicular, wavy and nuclear pseudopalisading arrangements and round cells with cystic lesions. The tumor cells invaded not only the brain but also the parietal bone. In the brain, the tumor cells infiltrated diffusely into the leptomeningeal and perivascular spaces and parenchyma, in which the tumor cell morphology and invasive pattern closely resembled those of malignant astrocytoma and malignant reticulosis. Immunohistochemically, the tumor cells in the masses showed positive reactions for both S-100 protein and GFAP, while those in the cerebral invasion sites were negative for GFAP and less positive for S-100 protein. Electron microscopically, a single basal lamina layer and short intricate cell processes were confirmed in the tumor cells. From these results, the present tumor was diagnosed as a malignant schwannoma arising in the cranial cavity, probably originating from the trigeminal nerve. The present tumor is considered to be a relatively unique malignant schwannoma based on its growth and invasion patterns. (J Toxicol Pathol 2009; **22**: 139–142)

Key words: malignant schwannoma, cranial cavity, spontaneous, rat

Although malignant schwannomas arise spontaneously in various tissues of the body in rats and occasionally infiltrate into surrounding tissues[1–7], intracranial schwannoma rarely occurs, and therefore only limited information is available in the literature[5–7]. On the other hand, pituitary anterior tumors and astrocytomas are familiar tumors in the rat cranial cavity[8]. Occasionally, malignant pituitary tumors slightly invade the brain parenchyma and sphenoid bone[9, 10], while most malignant astrocytomas extensively invade the surrounding parenchyma and meninges, without growing out of the brain[11].

We encountered a case of spontaneous intracranial malignant schwannoma in a rat that severely invaded the brain and parietal bone and formed several masses in a region distant from the original site. In the present paper, we examine its histological and immunohistochemical characteristics.

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The animal was a male Crl:CD(SD) rat purchased from Charles River Laboratories Japan, Inc. (Kanagawa, Japan) and was subjected to a 26-week toxicity study. The present tumor was judged to be spontaneous in nature because no adverse effects of the test substance were detected in the test group including this animal. The animal was housed individually in a wire mesh cage under controlled conditions (23 ± 3°C room temperature, 50 ± 20% relative humidity and a 12-H light/dark cycle) and was given CRF-1 diet (CLEA Japan, Inc., Shizuoka, Japan) and tap water *ad libitum*. The animal was routinely monitored for clinical signs once a day and was weighed once a week during the study period.

The animal died spontaneously at 28 weeks of age and exhibited convulsion, prone/lateral position and bradypnea just before death; its body weight decreased from 631 g to 566 g during the last 2 weeks. Macroscopically, three intracranial masses that were grayish-white with some dark red areas were observed. The locations of the masses are shown in Fig. 1. One mass (mass A), 10 × 10 × 5 mm in size, was located at the bottom of the cranial cavity and involved the trigeminal nerve and compressed the brain. The other two masses, 10 × 10 × 5 mm (mass B) and 5 × 5 × 2 mm (mass C) in size, were present in the parietal bone. Mass B

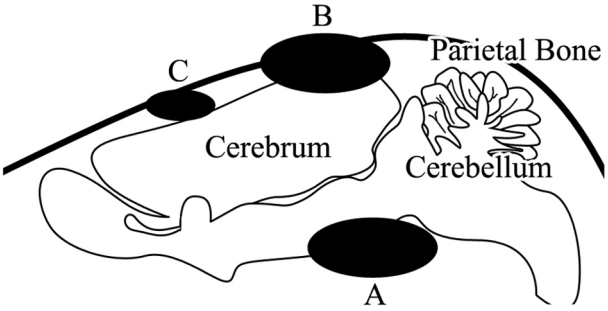

Fig. 1. Location of the intracranial masses. Mass A was located at the bottom of the cranial cavity, and masses B and C were in the parietal bone.

was difficult to separate from the cerebrum.

After complete necropsy, all tissues were fixed in 10% phosphate buffered formalin (pH 7.2), embedded in paraffin and cut into sections 2 μm thick. The tissues from the masses and surrounding bone tissue were decalcified with 10% formic acid solution and 10% formalin. Sections were stained with hematoxylin and eosin (HE) for histological examination. For immunohistochemical examination, selected sections were subjected to the labeled polymer method using an EnVision kit (Dako Japan, Kyoto, Japan) for anti-rabbit S-100 protein (1:500, Dako Japan) and anti-rabbit glial fibrillary acidic protein (GFAP; 1:500, Dako Japan) and were counterstained with hematoxylin. For electron microscopic examination, small pieces of tumor tissues fixed with 10% formalin were refixed in glutaraldehyde fixative, post-fixed in osmium and then routinely processed and embedded in epoxy resin (Oken Shoji, Tokyo, Japan). Ultrathin-sections of the selected areas were double-stained with uranyl acetate and lead citrate and examined under a JEOL 1200 EX electron microscope (Nippon Denshi, Tokyo, Japan).

Microscopically, the masses were not circumscribed with a distinct capsule and consisted of both fusiform and round cells in various proportions. The fusiform cells had oval to elongated nuclei with eosinophilic cytoplasm and were arranged with interlacing fascicles and occasionally with nuclei exhibiting a wavy pattern and pseudopalisading (Fig. 2a). In comparison, the round cells had round to oval nuclei with scanty cytoplasm, were closely packed and occasionally formed cystic lesions (Fig. 2b). The tumor cells developed along the cranial bone showed a sheet-like proliferation and partially invaded the brain, cranial bone and pituitary gland. In the cerebrum (Fig. 2c), the tumor cells proliferated in the leptomeningeal and perivascular spaces of the cerebral cortex, hippocampus, thalamus and mamillary body and in the subependyma of the third ventricle and invaded sparsely or focally the parenchyma, including the corpus callosum, thalamus and hippocampus. In the cerebellum (Fig. 2d), the tumor cells proliferated in the leptomeningeal and perivascular spaces of the cortex and invaded the cortical and medullary parenchyma.

Immunohistochemically, the tumor cells in the masses were generally positive for S-100 protein (Fig. 2e) and partially positive for GFAP (Fig. 2f). Conversely, in the brain, infiltrating tumor cells were negative for GFAP, and only a few of them were positive for S-100 protein. Reactive astrocytes showed positive reactivity for both S-100 protein and GFAP. Although most of the reports of immunohistochemical examinations have described malignant schwannomas in rats as positive for S-100 protein and negative for GFAP[3,6], Turusov[12] reported that the tumor cells in BDVI rats showed positive reactions for both S-100 protein and GFAP. In the present case, the tumor cells showed different immunohistochemical behaviors for S-100 protein and GFAP in the masses and invaded sites within the brain; positive reactions were observed for both S-100 protein and GFAP in the tumor masses, and positive reactions were observed only for S-100 protein in the invaded sites within the brain. The reason for such differences is still unclear.

Ultrastructually, the tumor cells contained poorly developed organelles, including mitochondria, rough endoplasmic reticula and free ribosomes. Short intricate cell processes and a single pericytoplasmic basal lamina layer were occasionally observed (Fig. 3). Taken together with the results of the histological and immunohistochemical examinations, the present tumor was diagnosed as a malignant schwannoma arising in the intracranial cavity, probably in the trigeminal nerve.

The present tumor probably originated from peripheral nerve fibers located in the base of the cranial cavity, especially the trigeminal nerve, which was embedded in the tumor. Prior to this report, 3 cases of spontaneous malignant schwannoma of the trigeminal nerve have been reported in rats aged less than 32 weeks old[5–7]. In one of these cases, the brain and spinal cord were invaded[6]; however, invasion into the parietal bone and formation of a tumor mass at the invasion site were not reported.

Interestingly, in the present case of spontaneous intracranial malignant schwannoma, the invasive manner in the cerebrum was quite similar to those of astrocytoma and malignant reticulosis, which infiltrate into the leptomeningeal and perivascular spaces and proliferate in the parenchyma of the brain[11]. Therefore, attention should be paid to correct diagnosis of these tumors, especially when only limited numbers of tissues samples are available.

In conclusion, the present case was generally consistent with previously reported malignant trigeminal schwannomas[5–7] but was unique in terms of formation of multiple masses in the cranial cavity away from the presumptive primary site. It also appeared to be highly invasive in the brain and was morphologically similar to astrocytoma and malignant reticulosis.

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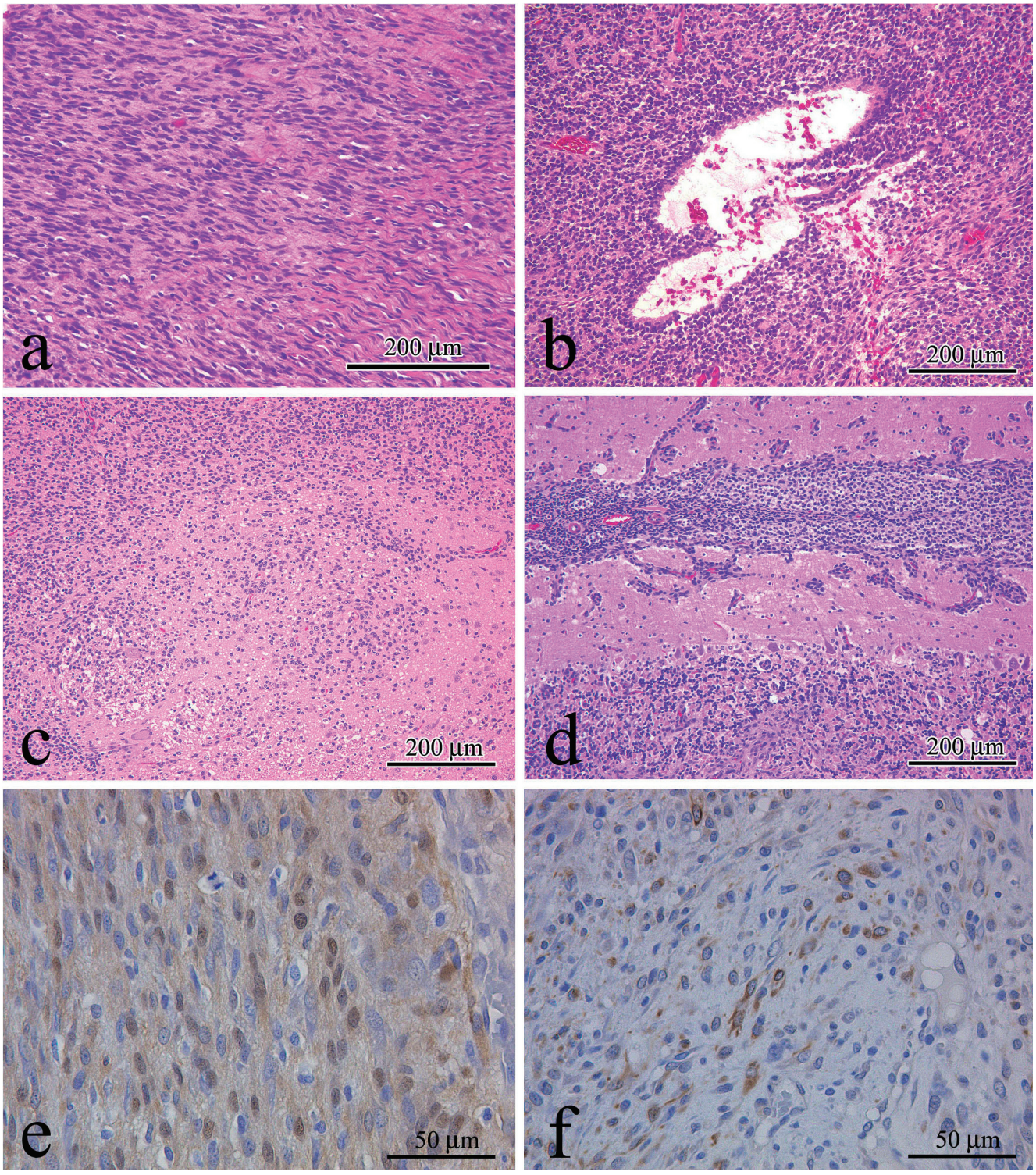

Fig. 2. a: Histological picture of mass B. The fusiform cells were arranged with pseudopalisading of nuclei and a wavy pattern. HE stain. b: Histological picture of mass A. The round cells formed a cyst. HE stain. c: The cerebrum. The tumor cells invaded diffusely into the parenchyma. HE stain. d: The cerebellum. The tumor cells proliferated in the leptomeningeal and perivascular spaces. HE stain. e: Immunohistochemistry for S-100 protein. The tumor cells from mass B showed positive reactions in the cytoplasm and nuclei. f: Immunohistochemistry for GFAP. The tumor cells from mass B showed positive reactions in the cytoplasm.

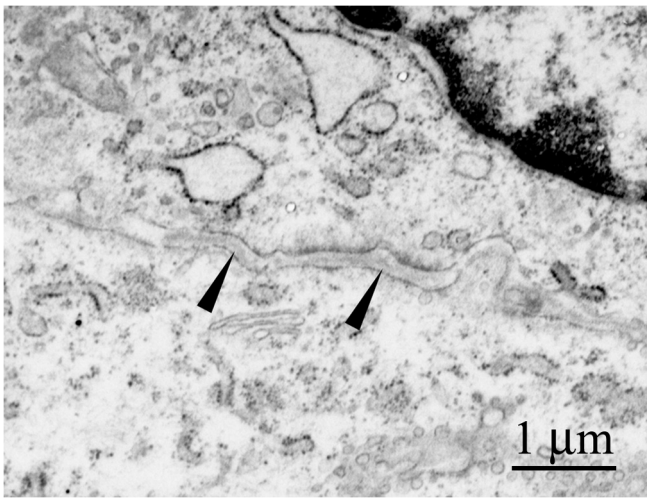

Fig. 3. Ultrastructure of the tumor cells. A single pericytoplasmic basal lamina layer (arrow heads) was observed.

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