Case Report

MALIGNANT SCHWANNOMA OF THE INTRACRANIAL TRIGEMINAL NERVE IN A 19-WEEK-OLD FEMALE SPRAGUE-DAWLEY RAT

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Abstract: Light microscopic, histochemical and ultrastructural observations were conducted to examine a spontaneous malignant schwannoma arising from the intracranial trigeminal nerve in a 19-week-old female virgin Sprague-Dawley rat. The tumor, which extended from the right trigeminal ganglia and nerve to the bottom of the cerebellum macroscopically, was composed of sheets of small fusiform cells with rod-shaped nuclei and rather abundant eosinophilic cytoplasms. Some tumor cells were arranged in roughly parallel arrays with nuclear palisades or in a whirling pattern. The tumor had invaded the subarachnoid and Virchow-Robin's space of the cerebrum and thoracic spinal cord, and the pars distalis of the pituitary gland. In immunohistochemistry, the tumor cells showed positive reaction to anti-S100 protein and anti-vimentin, but were negative for anti-GFAP. Ultrastructurally, interdigitating cytoplasmic processes, a few junctional complexes, and fragmented basal lamina-like structures were observed. These findings closely resembled the malignant schwannoma described in the soft tissues of rats and human. From our review of the literature, we believe our case to be the first report of a spontaneous malignant schwannoma arising in the intracranial trigeminal nerve of a young rat. (J Toxicol Pathol 9: 107-112, 1996)

Key words: Spontaneous tumor, Malignant schwannoma, Trigeminal nerve, Intracranial tumor, Young rat

Introduction

The incidence of spontaneous intracranial tumors in rats is very low except for pituitary neoplasms. Pituitary tumors are very common neoplasms in various rat strains such as SD1-3 and F3444,5. The next most familiar tumors in the cranial cavity are brain tumors, but review of the literature shows that the incidence is 0.1 to 3.3% with a tendency to occur among aged rats1-3,6-14. In contrast, quiet a few papers11 have been reported concerning the tumors of intracranial peripheral nerve in aged rats. In the present study, a spontaneous malignant schwannoma arising from the intracranial trigeminal nerve in a young Sprague-Dawley (SD) rat is reported.

Materials and Methods

Our case was a female rat of Jcl: SD (CD) strain. The animal was one of the untreated control group in a subacute toxicity study for safety assessment in the Toxicology Research Laboratories of Fujisawa Pharmaceutical Co., Ltd. The animal, which was housed in a stainless steel cage under barrier conditions at 23±2°C room temperature, 55±5% relative humidity, and a 12-hr light-dark cycle, had been given standard radiation-sterilized laboratory CA-1 diet (CLEA Japan, Inc., Tokyo) and chlorinated tap water ad libitum. The animal was routinely observed for clinical signs twice a day and weighed once a week during the study period, and
was carefully necropsied at 19 weeks of age according to the study schedule. Over 40 of the animal’s organs including an intracranial tumor detected at necropsy were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin-eosin (HE) for routine histopathologic examinations. Additional cross sections of the brain and trigeminal nerve containing a tumor mass were stained with periodic acid–Schiff (PAS) and were immunostained with a labelled–streptavidin–biotin method (LSAB2 universal kit, Dako, Glostrup, Denmark) using anti-cow S100 protein (1:400 in dilution, Dako), anti-human GFAP (1:100, Dako), anti-swine vimentin (V9, 1:40, Dako), and anti-keratin/cytokeratin (AE1, AE3, prediluted, Nichirei, Tokyo, Japan) antisera. For ultrastructural observations, some of the formalin–fixed tumor tissues were cut into small pieces, post fixed doubly in glutaraldehyde and osmium tetroxide, embedded in epoxy resin, sectioned, and double-stained with uranyl acetate and lead citrate.

Results

The animal grew normally until it was 13 weeks old, when its body weight was 304 g, and then wasted to 148 g at 19 weeks of age, showing such clinical abnormalities as decrease of food consumption, staggering gait, abnormal respiratory sound, and decreased spontaneous motility (Fig. 1). In gross observation, the tumor was observed as a yellowish-white gelatinoid mass $5 \times 10 \times 10$ mm in size, located from the right trigeminal nerve to the bottom of cerebellum; it had involved and compressed the neighboring cerebrum and pituitary gland with hemorrhage. Of the other organs and tissues, the majority observed were normal, but multiple dark-red foci of the lung and atrophy of the liver and that of such lymphatic organs as spleen, thymus, and mesenteric lymph nodes were detected.

Light microscopy showed that the tumor was located in the trigeminal nerve, the trigeminal ganglia containing the remaining non-neoplastic ganglion cells, medulla of the cerebellum, pons, and bulb but without any capsulation (Fig. 2-a, b, c). Although the tumor cells infiltrated the subarachnoid and Virchow–Robin’s space of both cerebrum and thoracic spinal cord (Fig. 3-a, b), and pars distalis of the pituitary gland, they did not invade the parenchyma in the cerebrum or spinal cord. The tumor showed sheets of small fusiform cells with rod-shaped and hyperchromatic nuclei and abundant eosinophilic cytoplasmids (Fig. 4-a, b). Some cells tended to be arranged in parallel arrays with nuclear palisades or in whirling pattern (Fig. 4-b). While the tumor cells showed weak-positive staining for PAS, they possessed no granular structures in the cytoplasm. Mitotic figures and hemorrhagic changes were frequently disseminated (Fig. 4-a), but edematous or microcystic lesions were scarce. Immunohistochemistry gave positive staining for S–100 protein and vimentin in most tumor cells, but no reaction for

![Bodyweight change](image)

**Fig. 1.** Bodyweight change and clinical abnormalities.
Fig. 2. A tumor mass in the cerebellum (a) and trigeminal nerve (b). The tumor cells had proliferated around the remaining non-neoplastic ganglion cells of the trigeminal ganglia (c). (a) HE, ×10, (b) HE, ×100, (c) HE, ×400.

Fig. 3. Infiltration of tumor cells in the thoracic spinal cord. (a) HE, ×40, (b) HE, ×300.
GFAP or keratin/cytokeratin. Electronmicroscopically, the tumor cells had oval or rod shaped nuclei with occasional irregular infoldings of the nuclear membrane. The cytoplasm contained a few organelles, such as mitochondria, rough endoplasmic reticulum, and free ribosome. Among the tumor cells, some interdigitating cytoplasmic processes and a few junctional complexes were observed (Fig. 5-a, b). Though mature collagen fibers were scarce in the intracellular areas, fragmented basal lamina-like structures were often seen (Fig. 5-b).

Careful pathological observations disclosed for eign body pneumonia and systemic atrophy of the femoral and sternal bone marrow, spleen, thymus, mesenteric and mandibular lymph nodes, liver, uterus, and skin. No pathological changes including distant metastasis of the tumor were observed in the other organs and tissues.
Discussion

Our case possessed such characteristic features as sheets of fusiform cells, sometimes in parallel array with nuclear palisades or in whirling pattern, and invasive growth to the central nerve. Moreover, the reaction to S-100 protein and vimentin in immunohistochemistry, as well as such electron microscopic features as interdigitating cytoplasmic processes, intercellular junctions, and basal laminae, were suggestive of schwann cell origin\textsuperscript{15,16}. These pathological appearances closely resembled the malignant schwannoma described in the soft tissue of rats\textsuperscript{15} and human\textsuperscript{16}. Based on the aforementioned findings and the anatomical location of the tumor, this tumor should be diagnosed as a malignant schwannoma arising from the intracranial trigeminal nerve.

The majority of peripheral nerve sheath tumors of the rat occur spontaneously in the subcutaneous tissues, especially of the ear, neck, head, and shoulder\textsuperscript{15}. Other tissues in which the tumors have been reported are the salivary gland, pituitary gland, stomach, body cavity, spinal cord, uterus\textsuperscript{15}, intracocular and orbital tissue\textsuperscript{17}. Although certain chemical carcinogens have been reported to induce peripheral nerve sheath tumors in association with the trigeminal nerve\textsuperscript{18-19}, there are quite a few papers\textsuperscript{11} concerning the spontaneous occurrence of this tumor occurred spontaneously in aging rats. Our case may resemble some of these tumors which have been reported, but the details are not available because of scant description.

In human, Horie et al\textsuperscript{20}, noted that most schwannomas of the intracranial trigeminal nerve are benign, and that there have been only 8 cases of malignancy without von Recklinghausen's disease, including his case. In contrast, rat trigeminal schwannomas\textsuperscript{18} including our case have been reported as having malignant potency. Whereas some authors\textsuperscript{13,21} described an etiologic relationship between intracranial tumors and clinical abnormalities, many rats bearing intracranial tumors scarcely showed clinical signs and there were no apparent explanations for the lack of unequivocal behavioral pathology in these papers. In our case, such abnormal signs as body weight loss and decreased food consumption, and systemic atrophic changes on pathological examination should be attributed to dystrophy due to dysfunction of the nervous parenchyma in view of the anatomical position of the tumor. Further, aspiration pneumonia might be related to paralysis of the trigeminal nerve, because of the close association between the trigeminal nerve and mastication\textsuperscript{22}.

It is generally agreed that intracranial tumors occur in aged rats\textsuperscript{5-14}. From the point of view of the occurring age 19 weeks, our case would be extremely rare. In our review of the literature, we found only two reports concerning intracranial tumors of young rats; these were a medulloblastoma of the cerebellum\textsuperscript{23} in a 14-week old Sprague-Dawley rat and a meningioma of the cerebrum\textsuperscript{24} in a 10-week old Wistar rat. Inclusive of our case, it is not known whether these were congenital. From our discussion, we believe our case to be the youngest SD rat having a malignant intracranial schwannoma arising from the trigeminal nerve.

References