BRIEF COMMUNICATION

Spontaneous Glioblastoma Multiforme in a Charles River CD Rat*

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The purpose of this report is to describe the occurrence and pathology of a spontaneous and rare brain tumor in a strain of rat commonly employed for drug and chemical safety testing. Glioblastoma multiforme is another term for “malignant astrocytoma” (Grade 3 or 4) and is characterized by cellular and nuclear hyperchromasia and pleomorphism, multinucleated giant cells and pallisading necrosis. The tumor exhibits highly aggressive invasive behavior. In contrast, “anaplastic glioma” is a term applied to any malignant tumor of glial cells including those containing astrocytes. Often, there are variable mixtures of cell types within a given tumor. None of these anaplastic gliomas exhibit the degree of anaplasia or invasive behavior seen in the tumor of this report.

Primary brain tumors in rats are infrequent compared to tumors found in other organ systems. In a recent report, astrocytoma was the most frequent glial cell tumor in Sprague-Dawley rats with an incidence of 28/2,630 in males and 18/2,765 in females (3). This literature report included a total of 88 brain tumors from 5,395 untreated controls and 297 brain tumors from a total of 19,251 rats examined in the combined control and treated groups. None of the astrocytomas reported satisfied the criteria needed for designation as glioblastoma multiforme.

A 1974 report of 38 naturally occurring brain tumors found in 41,000 Sprague-Dawley rats included 10 astrocytomas or malignant astrocytomas and 4 glioblastoma multiforme (9).

Other investigators (12) have shown that a high incidence of up to 100% brain tumors can be induced in Sprague-Dawley rats by multiple injection of small doses of methylnitrosourea (MNU) intravenously; and by administration of ethylnitrosourea to rats during pregnancy, approximately 50% of offspring developed brain tumors and all offspring developed peripheral nervous system tumors.

From these two reports, there were anaplastic gliomas induced that were characterized by either poorly differentiated astrocytes or pleomorphic oligodendrocytes. Both cell types were present when MNU was injected intravenously. None of the brain tumors were considered glioblastoma multiforme.

The glioblastoma multiforme of this report was found in a female rat sacrificed for humane reasons at 448 days of age after progressive weight loss of 145 g in the 5 preceding weeks, reduced physical activity and deteriorating general condition for the final 2 weeks. Although the rat was in a treated group of a 2-year study, there was no evidence of increased neoplasia or nonneoplastic disease associated with treatment in the study.

The tumor had a brown, lobular, well-circumscribed appearance with less clear distinction at the margins and had disrupted the normal appearance of the cerebellar architecture.

The tumor was seen first in 2 of the 3 routinely sampled coronal brain sections involving primarily the cerebellum where it was ovoid in cross-section about 1.5 cm across and had replaced most of the

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Fig. 1.—Photomicrograph of neoplasm showing focal necrosis, large cells with irregularly shaped nuclei and an area of smaller, more uniform cells resembling astrocytes. H&E. x400.

Fig. 2.—Photomicrograph contains large atypical cell and giant nucleus surrounded by smaller, more uniform cells with numerous mitoses. H&E. x600.
normal structure. The tumor extended rostradorsally to the posterior area of the cerebrum involving the dorsal sinus system, meninges and adjacent cerebral tissue and measured 0.4 x 0.8 cm irregularly rectangular on cut surface.

This highly malignant tumor appeared to replace most of the cerebellum with only a few cerebellar folia intact. Microscopically, the tumor also involved the dorsal vascular sinuses of the posterior cerebrum and adjacent brain tissue resulting in peritumor edema and focal malacia of both cerebral hemispheres. The tumor was densely cellular composed of undifferentiated astrocytes (Fig. 1). There was also pleomorphism associated with numerous, often large atypical mitotic figures and tumor cells with irregular hyperchromatic nuclei in which the astrocytic origin of tumor cells could not be recognized (Fig. 2). Prominent were large cells with hyperchromatic irregularly shaped nuclei and some with multinucleated or multilobulated forms.

Numerous variably sized irregular foci of incipient or more advanced liquefaction necrosis were found throughout the tumor accompanied in some by a formation resembling "pallisading." The degree of pallisading was variable but appeared similar in some foci to that shown in a detailed literature review of this tumor type (4).

There was a small area in the cerebellum where tumor cells of uncertain origin had small round to oval hyperchromatic nuclei and ill-defined cytoplasmic borders. Focal hemorrhage and edema were associated with this area of the tumor. There were numerous vessels, some of which were telangiectatic, in the tumor but they were not as prominent as the giant cells of the tumor. The vessels lacked the marked proliferation of the endothelium of small capillaries with formations resembling glomerular tufts. These tufts have been described previously for some forms of this tumor in animals and humans (7, 11). There was very little stroma throughout the tumor.

Astrocytoma in the rat is reported to occur more frequently in males than females with most tumors found after 79 or more weeks of age (1, 3, 8). The female rat of this report was 64 weeks old when killed in cachetic condition. Similar tumors, re-
FIG. 4.—Electronmicrograph of a malignant astrocyte adjacent to a capillary. Note pleomorphic nucleus (N), scarce organelles, and bundles of glial filaments (arrowheads). Myelinated nerve fibers (empty arrowhead). Formalin fixation. Lead citrate stain. ×10,375.

cently reported in the literature, were commonly found involving the cerebrum with fewer (approximately equal) numbers seen in the midbrain, cerebellum and medulla.

Electron microscopic examination of the tumor revealed tumor cells with dispersed nuclear chromatin, the absence of a nucleolus, hyaloplasm of low density due to a scarcity of organelles, cytoplasmic bundles of glial filaments, and close association with the surface of capillaries (Figs. 3, 4). These features are all characteristic of astrocytes (2, 6, 10). Because of formalin fixation the tumor cell outlines are poorly preserved, thus, the only ultrastructural finding that might indicate whether the neoplastic astrocytes are derived from fibrous or protoplasmic astrocytes is the configuration of the glial filaments. Fibrous astrocytes have glial filaments more dispersed while protoplasmic astrocytes have filaments occurring in bundles usually parallel to the long axis of the cell (6). This orientation of glial filaments can be seen (Figs. 3, 4) indicating the tumor cell origin is probably the protoplasmic astrocyte.

REFERENCES