2. EXPERIMENTAL INDUCTION OF GLIOGENOUS TUMORS

Sadao Kawai

Dept. of Pathol, School of Med., Gunma Univ.

Histological analysis and classification of gliomas are often clouded by diversity of cellular composition. This pleomorphic appearance has been ascribed to a variety of cell types involved in neoplasia, alterations in arrangement and shape of tumor cells produced by circulatory disturbances, and varying degrees of anaplasia. This is also a cause of controversy in the classification of gliomas. The experimental works of Zimmermann and his collaborators on the induction of gliomas in mice seems to give various important informations concerning the cytology of the gliomas and their classification. According to them, a considerable types of gliomas can successfully be produced. Even the medulloblastoma, which has been assumed to originate in the foetal granular cell layer of the cerebellum or in the nests of primitive cells arrested in the posterior vellum, is reported to be induced when the carcinogen is placed in the cerebellum. It is also pointed out that the location in which carcinogen in placed is an important determinant of the appearance or type of experimental gliomas. In order to produce brain tumor and to analyse cytological characters of the induced tumors, similar experimental works were carried out in our department with methylcholanthrene.

A total of 109 mice of C3H and ddN strain were employed in the first experiment. The methylcholanthrene pellet was implanted in the cerebrum or the cerebellum. Fifty six mice had survived over 94 days after the operation, 45 of which were found to have developed tumor. Of these tumors, 33 were sarcomas and 12 were gliogenous. Based upon the predominant tumor cells, the latter were subclassified into 7 glioblastomatous, 3 oligodendrogliomatous, 1 astrocytomatous tumor and 1 gliogenous tumor complicated by a pronounced proliferation of mesenchymal tumor cells. Average survival time of animals with gliogenous tumors was 251 days. Of these gliomas, 10 were situated in the cerebral hemisphere and 2 in the cerebellum. Various histological types, such as medulloblastoma, ependymoma and spongioblastoma polare were not found.
in this series of experiments. Of the 33 sarcomas, 29 were spindle-shaped cell sarcomas, 3 were giant cell sarcomas and 1 was pleomorphic cell sarcomas. Of these, 16 were conceived to have arisen intracranially. Subcutaneous transplantation was made into mice of the same strain. Four gliomas and 6 sarcoma produced in mice of C3H strain were successfully transplanted. It is shown that subtransplants revealed only minor histological variations from the original tumors with few exceptions of notable change. The subtransplant of astrocytomatous tumor showed transformation into glioblastoma with evidence of small necrotic foci surrounded by palisading tumor cell nuclei. A pronounced tendency to form rosette around blood vessels was found in the subcutaneous transplant of the glioblastomas. There was also a case in which glioblastoma changed into sarcoma after the second generation of transplantation.

The second work is now being carried out employing mice of ddN, CFI, and CFW strain, and Donryu rats. Up to this time, intracranial tumors have been produced in 7 of 96 mice and 4 of 97 rats (glioma in 8, sarcoma in 3). The histological features of the glioma group were those of glioblastoma, astrocytoma, oligodendroglioma and ependymoma. Two tumors were found replacing the cerebellum. However the tumor histologically suggestive of medulloblastoma has not yet been produced.

The study relating to the ultrastructure of the induced tumors has been pursued also simultaneously with an investigation of the histology. The electron microscopic observations on the sections of a tumor, classified by light microscopy as oligodendroglioma, disclosed the predominant tumor cells to be of neoplastic oligodendrocyte. They had irregularly shaped often infolded nuclei containing finely and uniformly granulated nuclear chromatin. The nucleolus was multiple. In contrast to normal oligodendrocyte, the cytoplasm was abundant and rather pale with relatively few organelles and distinct Golgi apparatus. The fine structure of predominant constituents of a tumor classified as astrocytoma was also suggestive of neoplastic astrocytes. Their nuclei were ovoid and watery with clumped chromatin masses. The cytoplasm was generally rather electron dense, containing increased number of organelles and fine osmiophilic granules. There was, however, a considerable variability in electron density of cytoplasm, watery to dark, from one cell to another.

From these observations, the following were concluded:

1) The experimentally produced gliomas were in majority composed of different cell type, that is, highly anaplastic glial cells and neoplastic astrocytes and oligodendrocytes, intermixed with different adult types of glia, microglial elements and with bipolar cells suggestive of mesenchymal origin, presenting pleomorphic microscopical appearance. In other words, they were “mixed”, as Zimmermann and his coworkers had repeatedly insisted.
2) The experimental evidence also suggests that pre-existing cells of neuroglial stroma as well as cells of mesenchymal origin have potentiality to share, through proliferation, in tumor formation in response to chemical carcinogen.

3) Because of a low glioma incidence and of unsuccessful production of a variety of histological types, the results hitherto obtained fail to give a significant contribution to the study on the site of predilection of gliomas in the brain.

4) Gliomas in the cerebellum developed in 3 cases. They showed features of glioblastoma or mixed tumor and were not histologically suggestive of medulloblastoma.

5) Electron microscopic observations revealed the mouse gliomas classified as oligodendroglioma and astrocytoma by light microscopy to be predominantly composed of neoplastic oligodendrocytes and astrocytes with considerable anaplasia.