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Disseminated Astrocytoma. A Neuropathologic Study

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ABSTRACT. Neuropathologic findings of a case of disseminated astrocytoma are described in a 47-year-old woman who had progressive mental deterioration, gait disturbance and urinary incontinence. She became comatose and tetraplegic in the later stage of a one year course.

Neuropathologically, the brain was of normal size and neoplastic astrocytes of low malignant nature and variable cellularity were scattered throughout the brain, which was examined from the frontal lobe to the medulla oblongata. The tumor cells were especially prominent in the subpial and subependymal regions.

Our case was thought to be intermediate between gliomatosis cerebri and multicentric glioblastoma.

Key words : Disseminated astrocytoma — Gliomatosis cerebri — Multicentric glioblastoma — Brain tumor — Neuropathology

A pathologic condition in which atypical astrocytes proliferate the whole brain diffusely is recognized as gliomatosis cerebri, diffuse gliomatosis or diffuse cerebral astrocytoma.[1—7] It has various other names such as patchy blastomatous infiltration of the central nervous system,[8] diffuse (cerebral) glioblastosis,[9—13] diffuse glioma of the brain,[14] gliomatous hypertrophy,[15] diffuse systemic blastomatous overgrowth of the glial apparatus of the brain[16] and so on. Formerly, this condition was thought to be a blastomatous type of diffuse sclerosis.[16] Afterward, Malamud and associates,[2] Moore,[10] Dunn and Kernohan,[3] and Russel and Rubinstein[17] recognized that this was a true neoplasm, identical with glioma.

On the other hand, some types of glioma, especially glioblastoma multiforme, are known to occur multicentrically, with an incidence of about 5 percent.[18]

We experienced a case of astrocytoma in which neoplastic astrocytes of low malignant nature and variable cellularity proliferated disseminatedly throughout the brain. The astrocytoma was different from both typical gliomatosis cerebri, showing diffuse neoplastic proliferation mainly in the bilateral cerebral white matter, and typical multicentric glioblastoma.

CASE REPORT

Clinical Course (B 47338)

A 47-year-old woman was admitted to the Kawasaki Medical School Hospital because of mental deterioration and gait disturbance on September 27, 1982.

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The patient was well until six months earlier, when she developed progressive weakness of the right upper and both lower extremities, and sensory disturbance of the right side of the face. Three months later she had deteriorated mentally and could not walk for weakness.

There was a history of operation for uterine myoma two years before admission.

Neurologic examination revealed that the patient was mentally dull and disoriented as to time and place. Horizontal nystagmus was seen bilaterally. Weakness was present in the right upper and both lower extremities. Deep tendon reflexes were hyperactive in the right lower extremity. There was mild hypesthesia on the right side of the face. She could stand up from a chair but hardly walk.

A lumbar puncture yielded watery clear cerebrospinal fluid under a pressure of 90 mm; the fluid contained 13 lymphocytes per cubic millimeter; the protein was 50 mg per 100 ml, and the glucose 66 mg per 100 ml. A computed tomographic (CT) scan of the brain disclosed an enhanced lesion with perifocal edema in the left temporal lobe and a small enhanced lesion in the head of both caudate nuclei, and coated enhancement along the wall of the right lateral ventricle after the intravenous administration of contrast material. The lateral and third ventricles were slightly enlarged. A tuberculin skin test was negative.

After admission, prednisolone was administered, but the patient's general condition deteriorated progressively. She no longer spoke and had urinary incontinence. Anisocoria was noted, with the left pupil larger than the right. Fundoscopic examination revealed no papilledema.

From November 17, 5,000 rads of radiation was irradiated to the whole brain over 56 days. In January, 1983, a hypotensive episode developed and her respiratory state became poor. The respiration was assisted. The white-cell count was 13,400. Soon she became comatose and tetraplegic. She died on February 23 in the same year, one year after the onset of the illness.

Pathologic Findings (A 83-30)

A general autopsy disclosed pulmonary edema, organizing pneumonia, fatty liver, 400 ml of clear fluid in the left pleural cavity and 300 ml in the right, and a gastric ulcer.

The brain weighed 1,080 g. The leptomeninges were thickened and slightly turbid. Coronal sections of the cerebral hemispheres revealed small softened lesions, yellow-brown in color, in the cortex of the left transverse gyrus and bilateral hippocampal gyri and amygdaloid nuclei. The lateral and third ventricles were slightly dilated. Cerebral parenchyma along their walls was tinged yellow-brown and had greater consistency. Several millet-sized nodules had projected into the ventricles (Fig. 1). Serial sections through the cerebellum and brainstem were unremarkable.

Microscopically, tumor cells with variable cellularity suggestive of atypical astrocytes were scattered throughout the brain, which was examined from the frontal lobe to the medulla oblongata (Fig. 2). They were relatively large and round, oval, elongated or irregular in shape. The nuclei were distorted, rich in chromatin, frequently multiple and had occasional cytoplasmic invaginations. The cytoplasm was eosinophilic and generally abundant. Perivascular spaces

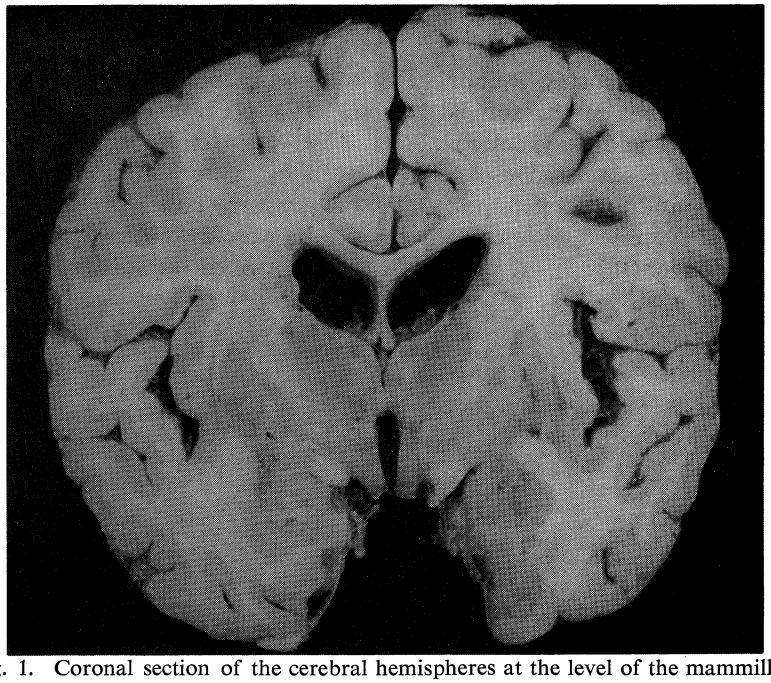

Fig. 1. Coronal section of the cerebral hemispheres at the level of the mammillary bodies showing small nodular lesions in the bilateral hippocampal gyri, amygdaloid nuclei and right caudate nucleus. The lateral and third ventricles are slightly dilated.

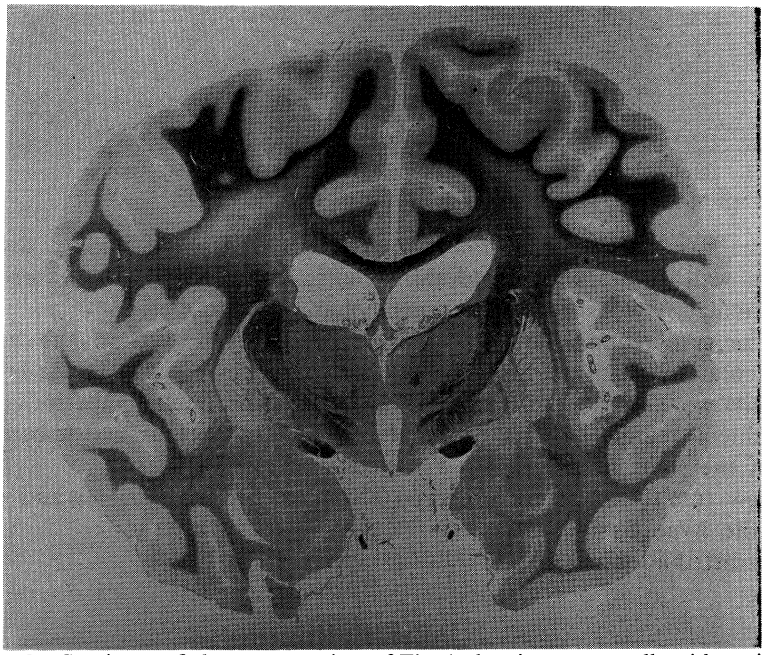

Fig. 2. Specimen of the same section of Fig. 1 showing tumor cells with variable cellularity scattered in the cerebral hemispheres, especially in the cerebral cortex and periventricular area. Klüver–Barrera, × 0.75.

in the tumor tissue were infiltrated by lymphocytes, but endothelial proliferations were not apparent.

In the cerebral cortex, tumor cells were clustered irregularly and were especially prominent in the subpial region. The left transverse gyrus, bilateral hippocampal gyri and amygdaloid nuclei, observed as softened lesions by gross examination, were almost completely replaced by tumor cells. In other areas of the cortex infiltrated by tumor cells, pre-existing cortical structures were generally well preserved, although the nerve cells were pyknotic and occasionally reduced in number (Fig. 3). A few tumor cells infiltrated the subarachnoid space.

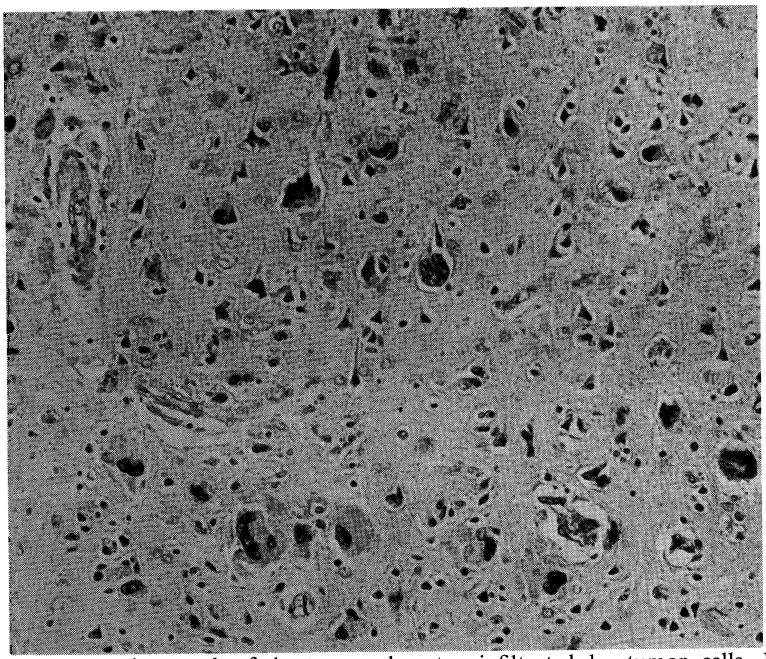

Fig. 3. Photomicrograph of the temporal cortex infiltrated by tumor cells. Pre-existing cortical structure is generally well preserved. HE, × 158.

In the basal ganglia and thalamus, tumor cells were mainly distributed along the wall of the lateral and third ventricles. Tumor cells extended into the ventricular cavities across the ependymal cell lining.

In the cerebellum, tumor cells were mainly observed in the cerebellar cortex, dentate nucleus and around the fourth ventricle (Fig. 4). In the brainstem, tumor cells were distributed mainly in the cerebral peduncles, superior colliculus, periaqueductal region, pontine base, inferior olivary nucleus and subependymal region of the floor of the fourth ventricle.

A few tumor cells were observed also in the optic chiasma and posterior lobe of the hypophysis.

The distribution of tumor cells is illustrated in Fig. 5.

DISCUSSION

Clinically, the patient showed mental deterioration, gait disturbance and urinary incontinence with some other focal signs. She became comatose and

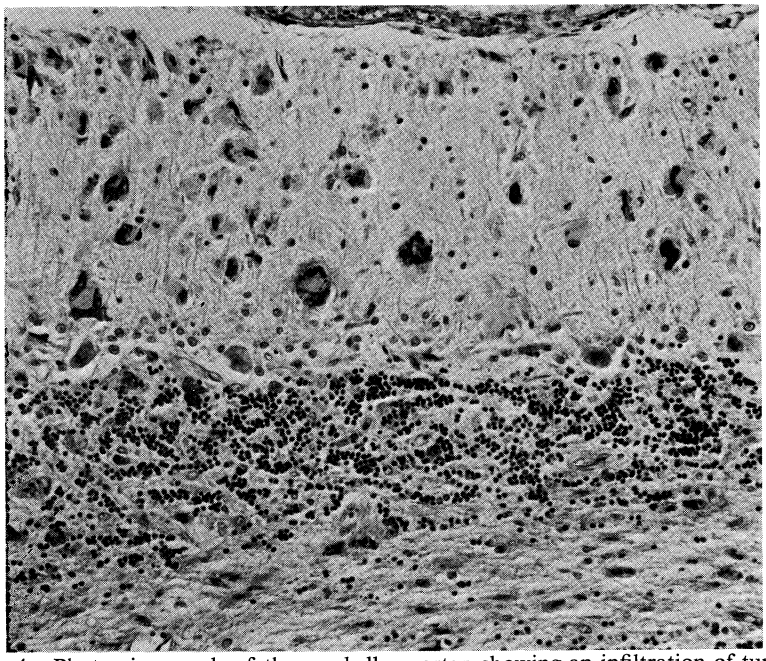

Fig. 4. Photomicrograph of the cerebellar cortex showing an infiltration of tumor cells. HE, × 158.

tetraplegic in the later stage, without symptoms and signs of increased intracranial pressure, and died of respiratory distress due to pulmonary edema one year after the onset of the disease. Although a brain tumor was suspected before her death, no localized mass was detected.

Neuropathologic examination revealed neoplastic astrocytes of low malignant nature and variable cellularity scattered throughout the brain. This pathologic process was considered to be malignant because of its prominent pleomorphism with occasional multinucleated giant cells.

The condition in which neoplastic astrocytes proliferate diffusely throughout the brain is recognized as gliomatosis cerebri.[1–7] In gliomatosis cerebri, however, neoplastic cells usually proliferate in the bilateral cerebral white matter[19] or diffusely in the whole brain including the spinal cord.[10,13] In our case, which was different from typical gliomatosis cerebri, neoplastic astrocytes proliferated disseminatedly with occasional small nodules, especially in the subpial and subependymal regions. The subpial and subependymal nodules may be the result of seeding of tumor cells through the cerebrospinal fluid from the primary lesion, but the extensive distribution of the tumor cells in the brain is more likely a result of astrocytes becoming neoplastic simultaneously in various places of the brain, as in the cases of Dunn and Kernohan.[3] In their cases also, a process of diffuse neoplastic transformation was suggested, instead of spreading from a primary focus. In our case, an immunodeficient state might have been responsible for these disseminated overgrowths of neoplastic astrocytes. As circumstantial evidence for disseminated overgrowth, many discrete lesions were observed in CT scans early in the course of the illness.

The distribution and nature of tumor cells in our case are also apparently

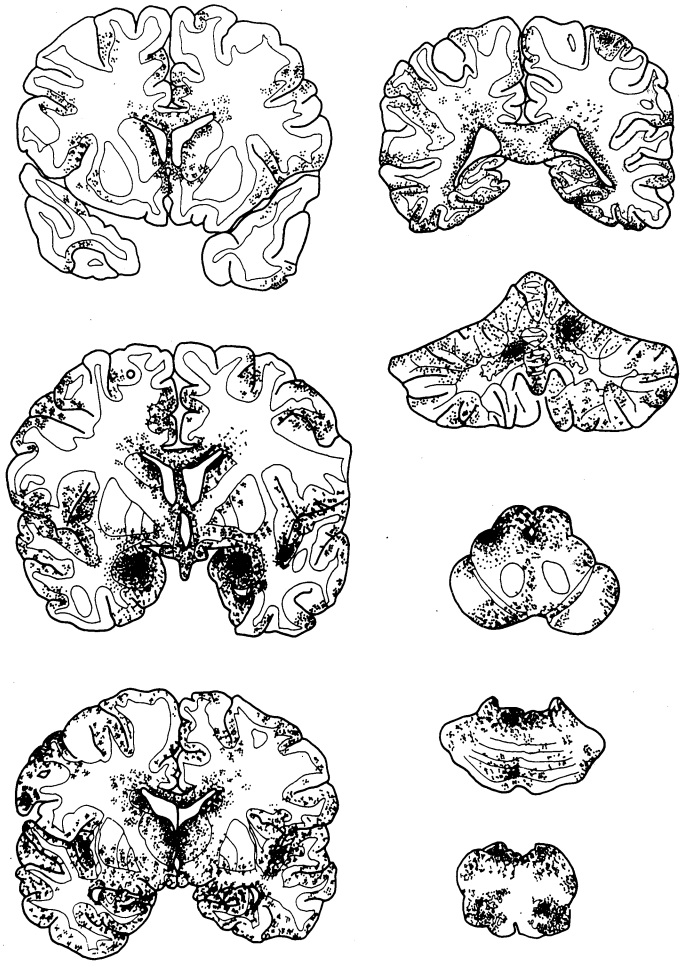

Fig. 5. Illustration of the distribution of tumor cells.

different from multicentric glioblastoma because of the relatively continuous neoplastic cell infiltration.

Clinical symptoms and signs of patients with gliomatosis cerebri are variable and frequently devoid of focal signs, with only mental and personality changes, and symptoms and signs of increased intracranial pressure,[20] reflecting the diffuse involvement of the brain. Our case showed focal signs such as weakness of the right upper and both lower extremities, and sensory disturbance of the right side of the face. The age of the patients in the literature is also variable, ranging from 9[21] to 77 years.[7] The duration of the disease varies from several weeks to several years. The present patient was a 47-year-old woman, and the duration of the illness was one year. Neuroradiological studies including CT scan do not reveal any pathognomonic findings, and only show diffuse brain swelling with narrowing of the ventricular system.[22,23] In our case, however, there was no brain swelling ; instead, some small enhanced lesions were observed in the temporal lobe and caudate nucleus. Upon postmortem examination, the

brain of our case proved to be rather atrophic and the small enhanced lesions in the CT scan to be nodules of tumor cells.

Our case may be an incomplete form of gliomatosis cerebri or more likely an intermediate form between gliomatosis cerebri and multicentric glioblastoma, and pertinently designated as disseminated astrocytoma.

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