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Childhood Glioblastoma Multiforme Mimicking Basal Meningitis -Report of An Autopsy Case-

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=Abstract=**Glioblastoma multiforme is a highly malignant neuroglial tumor rarely reported in children with several differences compared to the adult tumor. Its clinical diagnosis is sometimes difficult because most children do not have an antecedant history to herald the development of the tumor. We report a case of glioblastoma multiforme in a child that presented clinically and radiologically as a tuberculous basal meningitis, and turned out to be a glioblastoma multiforme involving the thalamus, hypothalamus and brainstem, and spreading massively through the leptomeningeal and ventricular spaces. A 6-year-old girl presented with non-projectile vomiting and mild fever on October 1990. Over the ensuing 6 months she was found to have hydrocephalus and blurring of vision. She was treated for possible tuberculous meningitis without any improvement. Repeated CSF smears, cultures, cytology and brain CT did not provide any clue to a specific diagnosis. She remained stationary until January 23, 1992 when she elappsed into coma at home and died after supportive management for 7 days. Postmortem examination showed widespread gray white coating or nodules over the cerebellar and cerebral convexities as well as the brain base. Serial sections revealed that the main lesion was located in the thalamus, hypothalamus, and brainstem. Microscopically, it was a glioblastoma multiforme consisting predominantly of anaplastic spindle cells.**

Key Words: *Glioblastoma multiforme, Childhood, Thalamus, Hypothalamus, Brainstem, Meningitis, Leptomeningeal spread.*

INTRODUCTION

Glioblastoma multiforme (GM) is a highly malignant neuroglial tumor which accounts for 6.5% (1.9-10.7%) of all primary intracranial neoplasms in childhood (Dohrmann *et al.* 1976) and 2.6% (0.6-7.9%) of all GM (Dohrmann *et al.* 1976; Farwell *et al.* 1977; Dropcho *et al.* 1987). Childhood GM is characterized by a high incidence of leptomeningeal spread and intratumoral hemorrhage, and a more favorable or similar prognosis relative to adult GM patients

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(Dropcho *et al.* 1987). It is also shown that there is a relatively low frequency of GM relative to anaplastic astrocytoma in children and a high incidence of second malignant neoplasms. The thalamic areas are involved in upto 25% of childhood brain tumors (Cheek and Taveras 1966). Moreover they are liable to spread horizontally to the optic apparatus and contralateral thalamus, and spread vertically to infiltrate the brainstem and cerebellum (Hirose *et al.* 1975; Bernstein *et al.* 1984; Dropcho *et al.* 1987).

We present an unusual case of GM involving the thalamus, hypothalamus, midbrain, pons, and cerebellum with diffuse leptomeningeal spread (LMS).

REPORT OF AN AUTOPSY CASE

A 6-year-old girl was admitted to Seoul National University Children's Hospital (SNUCH) because of headache and abdominal distention on July 23, 1991. She first presented with abrupt but not projectile, recurrent vomiting since October 1990. Headache and mild fever were associated one month later. Lumbar puncture revealed some inflammatory cells and brain CT showed hydrocephalus. Antibiotic therapy relieved the above symptoms. However vomiting recurred in January 1991 and weight loss was detected. Repeated lumbar puncture exhibited an increased intracranial pressure (IICP) with no cells. She underwent a ventriculo-peritoneal(VP) shunt operation in May 1991 after brain MRI which showed suggestive tuberculous meningitis or tumor. Shunt revision was done due to paraparesis and blurred vision. In June 1991, she developed abdominal distention. Lumbar puncture revealed protein 1,775 mg%, glucose 54 mg%, and 380 cells/mm^3 with 80% lymphocytes. She was treated with antibiotics and anti-tuberculous drugs for 3 weeks and was transferred to SNUCH for further management. Physical examination revealed a chronically ill but alert girl with VP shunt reservoir in the right parieto-occipital area. The head was normocephalic and pupils were anisocoric (right 3 mm ; left 4 mm) but light reflex was prompt. Abdominal circumference measured 57 cm and shifting dullness was noted. Neurological examination showed no nystagmus and full extraocular muscle movement except for a slight limitation on upward gaze. Visual acuity was decreased more in the left than in the right. Motor and sensory functions and deep tendon reflexes were within mormal limits. Acid fast bacilli had never been found in smears and cultures of cerebrospinal fluid (CSF) and ascites. Brain CT after admission showed a suspicious but not definite lesion in the pineal area. Hydrocephalus became more aggravated compared to the previous CT which suggested shunt malfunction. Fundoscopy showed optic atrophy. Abdominal sonography showed massive ascites. Ascites tapping showed protein 725 mg%, glucose 95 mg%, 10 red blood cells and 45 leukocytes. CSF showed persistent increase of protein over 600 mg%. Repeated cultures of CSF and ascites were negative. The patient was kept on anti-tuberculous medication. Repeated VP shunts and a ventriculo-atrial shunt were done. Her condition remained stationary. She was brought to the emergency room in comatose state on January 23, 1992. She did not respond to painful stimulus. Pupils were fixed in midposition. Mannitol administration and intensive supportive care were done without effect. She expired on February 2, 1992.

Autopsy finding

Restricted autopsy of the brain was done 4 hours after her death. Cerebral hemispheres measured 15 cm in antero-posterior diameter (APD), 13 cm in biparietal diameter, 10 cm in height, and 1,080 gm in weight. Cerebellum measured 7.6 cm in APD, 10 cm in width, 7.2 cm in height, and 200 gm in weight. There was widespread chalky-white coating or nodules over the brainstem and cerebellum as well as the brain base (Fig. 1). Multifocal patchy lesions were located over the cerebral hemispheres and leptomeninges. Coronal sections of the

cerebrum and horizontal sections of the brainstem revealed a poorly demarcated gray-white, soft to firm tumor involving the thalamus, hypothalamus, midbrain, pons, and cerebellum (Fig. 2). The lesion frequently showed necrosis and cystic change. Subarachnoid spaces were diffusely and irregularly thickened, and measured 1.2 cm at maximal thickness. Ventricles were dilated with periventricular infiltration. On microscopic examination, the tumor mass consisted of bizarre plump or spindle cells with homogeneous, eosinophilic cytoplasm (Fig. 3). Mitoses were frequently found with occasional atypical forms. There were one or more amphophilic nucleoli. Geographic or palisading necroses were occasionally noted (Fig. 4). Spindle cells were arranged in whorling or interdigitating patterns with a mixture of bizarre tumor cells and various inflammatory cells (Fig. 5). In these areas, there was some delicate collagen meshwork amongst the tumor masses. Capillaries showed endothelial proliferation. Immunohistochemical study was

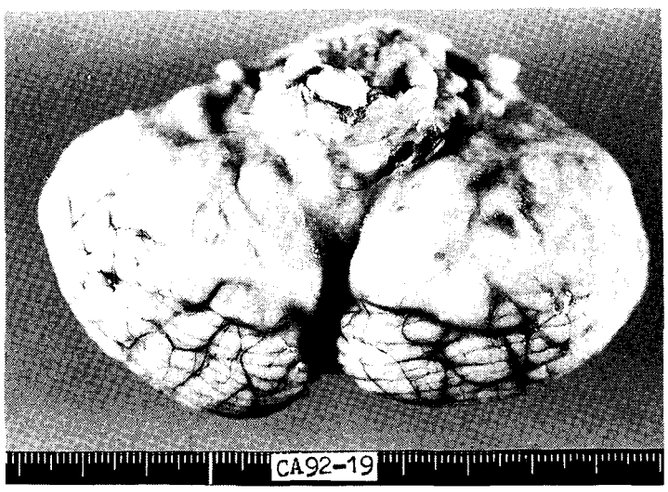

Fig. 1. Superior view of the cerebellum shows diffuse irregular gray-white "sugar coating" along the leptomeningeal spaces.

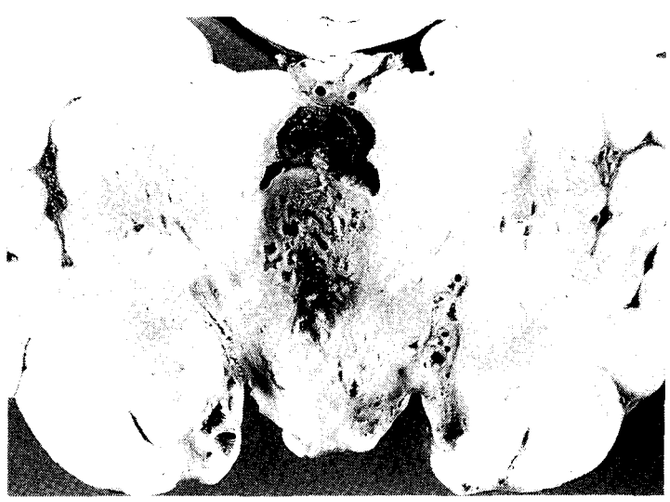

Fig. 2. A coronal section of the cerebral hemisphere reveals an ill-defined tumor involving the thalamus and hypothalamus. The tumor shows necrosis, hemorrhage, and cystic change.

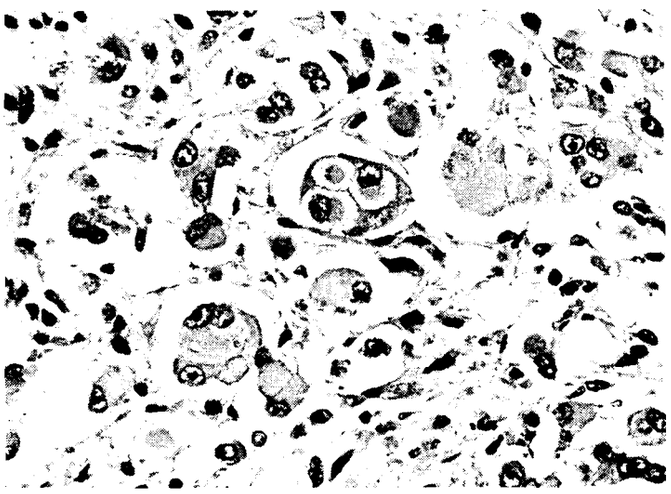

Fig. 3. High power photomicrograph of the tumor shows varying sized bizarre plump tumor cells with abundant eosinophilic cytoplasm, distinct nuclear membrane and prominent nucleolus.

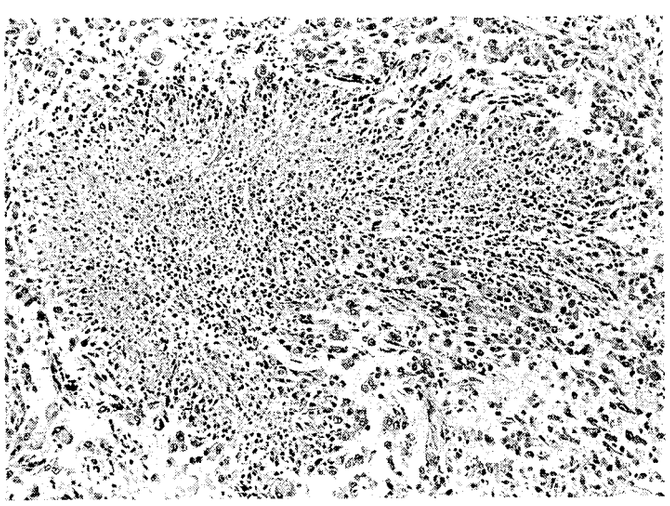

Fig. 4. Low power photomicrograph shows typical geographic or pseudopalisading necrosis.

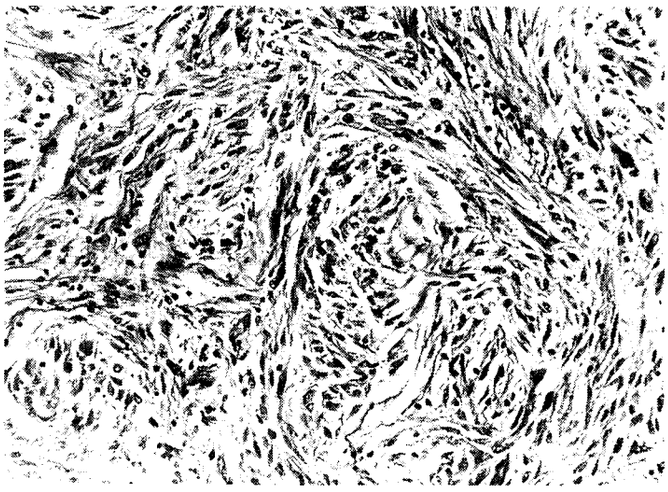

Fig. 5. Spindle cells are arranged in the whorling or storiform patterns (Masson's trichrome stain).

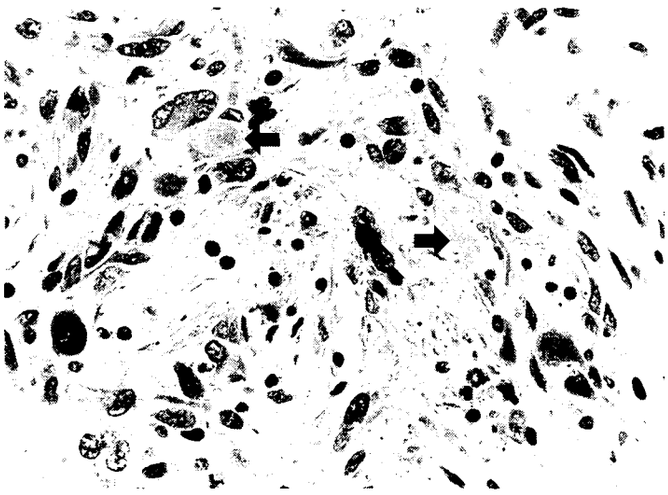

Fig. 6. Immunohistochemical stain for glial fibrillary acidic protein reveals strong reactivity in both plump and spindle tumor cells. A few Rosenthal fibers (arrows) show positive reaction (Avidin-biotin peroxidase complex method).

performed in both spindled or pleomorphic areas. Glial fibrillary acidic protein, S-100 protein, and α-1-antitrypsin were positive in both areas (Fig. 6). Other markers including vimentin, myoglobin, desmin, cytokeratin, and epithelial membrane antigen were all negative. Ultrastructurally, the tumor consisted of large epithelioid cells with round to oval nuclei. The chromatin was finely dispersed with a peripheral condensation. The cell borders were relatively well defined with no definite junctional complex. Straight or branching intermediate microfilaments were noted in the cytoplasm. A few tumor cells showed abundant Rosenthal fibers. Collagen fibrils were often seen in the intercellular spaces.

DISCUSSION

Childhood GM has two characteristic courses, and each of which is related to the location of the tumor (Dohrmann *et al.* 1976). GM of the brainstem or thalamus, a more primitive part of the central nervous system, occurs at a younger mean age (6.7 years) and has a shorter mean survival (6 months) relative to that of the cerebral hemispheres (12.7 years and 14.5 months, respectively). But Dropcho et al. reported that there was no significant difference between the survival curves for the patients with hemispheric tumors (119 weeks) versus thalamic or basal ganglia lesions (85 weeks). Thalamic tumors are more common in children than in adults. It is clinically characterized by relatively short duration of symptoms, high rate of occurrence of disorders of motor function, and IICP as part of the early illness (Hirose *et al.* 1975). Traditionally it has been thought to be "untouchable" because of its anatomical location (Bernstein *et al.* 1984). Most tumors arising in the thalamus are glial in origin (Cheek and Taveras 1966). The treatment of this lesion has been generally considered to be palliative (Hirose *et al.* 1975), because it showed frequent tumor extension and spread, both horizontally, to involve the optic apparatus and contralateral thalamus, and vertically, to involve the brainstem. There are three modes of tumor spread; 1) along white matter pathways; 2) subependymal; and 3) via CSF pathways (Bernstein *et al.* 1984). It is uncertain whether the thalamus, hypothalamus or midbrain is the accurate primary location in our case because of extensive tumor spread. Nevertheless, we regarded this lesion as a primary thalamic and hypothalamic tumor because pineal lesion was suspected in the first brain CT. Moreover, the thalamus and

hypothalamus were the site of the main tumor and had the largest dimensions grossly.

Massive LMS before the diagnosis shown in our case is a feature of primary central nervous system tumors of childhood (Packer *et al.* 1985; Russell and Rubinstein 1989). The rate of LMS is 30% and the diagnosis of LMS is confirmed by CSF cytologic examination or by characteristic findings on the CT scans and myelography (Kim *et al.* 1982; Jaeckle *et al.* 1985; Dropcho *et al.* 1987). The outcome in patients with LMS is generally poor. Of the 60 patients with LMS in one large series, 50 are dead and the median length of survival is 6 months (Packer *et al.* 1985). It is very unusual that repeated CSF smears, brain CTs and MRIs over one year could not localize the tumor in our case. This might be due to its macroscopic features of diffuse gliomatosis cerebri pattern. In spite of diffuse meningeal thickening on the brain CT and MRI, tumorous lesion was considered the last choice in differential diagnosis. This type of brain tumor, although be undetectable after intensive work-up by modern diagnostic methods, has not been described in literatures. Tuberculous meningitis had been the clinical diagnosis because it has been the most common cause of brain base lesion in Korea. Lower pons, medulla oblongata, and upper cervical spinal cord are "silent" in comparison to cerebral hemispheres, brainstem, and cerebellum. There was no tumor invasion into the medulla oblongata and upper cervical cord grossly and microscopically. This might be associated with the repeated negative results of the CSF examinations. Microscopically, we included gliosarcoma and meningeal sarcoma as well as malignant triton tumor in differential diagnosis because of the predominant spindle cell element. However collagen component was scanty in Masson's trichrome stain and immunohistochemical results supported the diagnosis of GM. Additionally, electron microscopic findings were also suggestive of the glial origin.

Based on this case, we have put special emphasis on intensive diagnostic trials to localize the tumor in the patients with prolonged increased intracranial pressure and uncontrolled meningitis despite absence of visible lesions by radiologic examination.

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