

Diffuse Cerebrospinal Gliomatosis with Extensive Leptomeningeal Spread

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Abstract

A case of diffuse cerebrospinal gliomatosis with extensive leptomeningeal spread is presented. The patient, an 18-year-old girl, was admitted due to progressive weakness and paresthesia of both legs, following rapid neuropsychiatric deterioration. An initial magnetic resonance imaging (MRI) study of the T-spine showed diffuse high signal intensities from T9 to T12 spinal cords on a T2 sagittal image and diffuse cord bulging at T1WI. This suggested an inflammatory lesion such as tuberculosis or fungal meningoencephalitis. A limited autopsy was performed. A microscopic examination revealed multifocal GFAP-positive astrocytic proliferations that were low grade astrocytoma in the cerebral leptomeninges, parietal, occipital and temporal lobes and anaplastic astrocytoma in the spinal cord and spinal leptomeninges. The high proliferative indices of the spinal lesion and aneuploidy correspond to a diagnosis of malignant astrocytoma and a rapid fatal clinical course.

Key Words: Cerebrospinal gliomatosis, subarachnoidal, leptomeningeal, meningoencephalitis, flow cytometry

INTRODUCTION

Diffuse cerebrospinal gliomatosis is a very rare entity, the third type of gliomatosis cerebri and it denotes an extensive glioma involving the supratentorial compartment, posterior fossa, and even the spinal cord. Moore described the first case of diffuse cerebrospinal gliomatosis masked by syphilis in 1954.¹ The clinical manifestations are variable consisting of motor weakness, sensory change, behavioral and mental changes that mimic motor neuron disease²⁻⁴ and meningoencephalitis. There is no specific radiologic finding for the condition. Clinical diagnosis is therefore impossible and a tissue biopsy is necessary for the diagnosis.

We present an autopsy case of diffuse cerebrospinal gliomatosis predominantly involving the spinal cord, which demonstrated a high proliferating activity of

the tumor cells, corresponding to a rapid fatal clinical course.

CASE REPORT

An 18-year-old girl was admitted to the hospital because of progressive weakness and paresthesia of both legs. The patient had been well until two months before admission, when she began to experience a painful sensation similar to electrical stimulation on both feet. Fifteen days before admission, the patient developed a headache on the posterior head. One week before admission, paresthesia and weakness of the legs worsened and the patient had difficulty climbing stairs. There was no recent history of chills, cough or diarrhea, although she displayed temporary facial twitching and tinnitus 3 days before admission. Upon neurologic examination, the patient was alert and oriented. Cranial nerve functions were preserved. Motor power was 5/5 in the upper extremities without drift; the lower extremities were partially paralysed; leg strength was 2/5 in both hip flexors; 4/5 in the quadriceps, hamstrings, dorsiflexors, and plantarflexors of the feet. She reported normal sensation in the upper extremities. There was marked dysesthesia below the level

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of T11 upon pin prick test. Temperature and vibration sensations were 50% of normal below the level of T11 and the joint position was slightly impaired. Deep tendon reflexes were +++ in the lower extremities and ++ in the upper extremities; bilateral Babinski signs were not noted.

The results of the lumbar puncture are presented in Table 1. Blood chemistry and urinalysis were normal. The levels of urea nitrogen, creatinine, bilirubin, calcium, alkaline phosphatase, and uric acid were normal, as were tests for α -fetoprotein and CEA. Serum total protein and albumin were 8.3 g/dl (nl: 6.0–8.0) and 5.6 g/dl (nl: 3.3–5.3), respectively. Serum electrophoresis revealed slightly increased albumin and total protein levels. Tests for antibodies to the human immunodeficiency virus, and VDRL were negative, as were tests for varicella antibody and Epstein-Barr virus antibody in serum and cerebrospinal fluid. Skin tests for *Paragonimus westermani* and *Clonorchis sinensis* were negative. The brain stem auditory evoked potential and median nerve soma-

Table 1. Results of Lumbar Puncture Findings

Variable	First admission	Second admission
Opening pressure (mmHg)	300	260
Glucose (mg/dl)	44	
Total protein (g/dl)	5.3	4.5
Red cells (mm ³)	1	10
White cells (mm ³)	45	
polymorphonuclear cells		
mononuclear cells	93%	
eosinophils		
others	7%	
Cryptococcal Ag	negative	negative
ADL (u/L, 37°C)	16.0	
Cytology	cell paucity	negative
Oligoclonal band	negative	
ELISA tests*	negative	

* ELISA tests for cysticercus, paragonimus, sparganum, clonorchis.

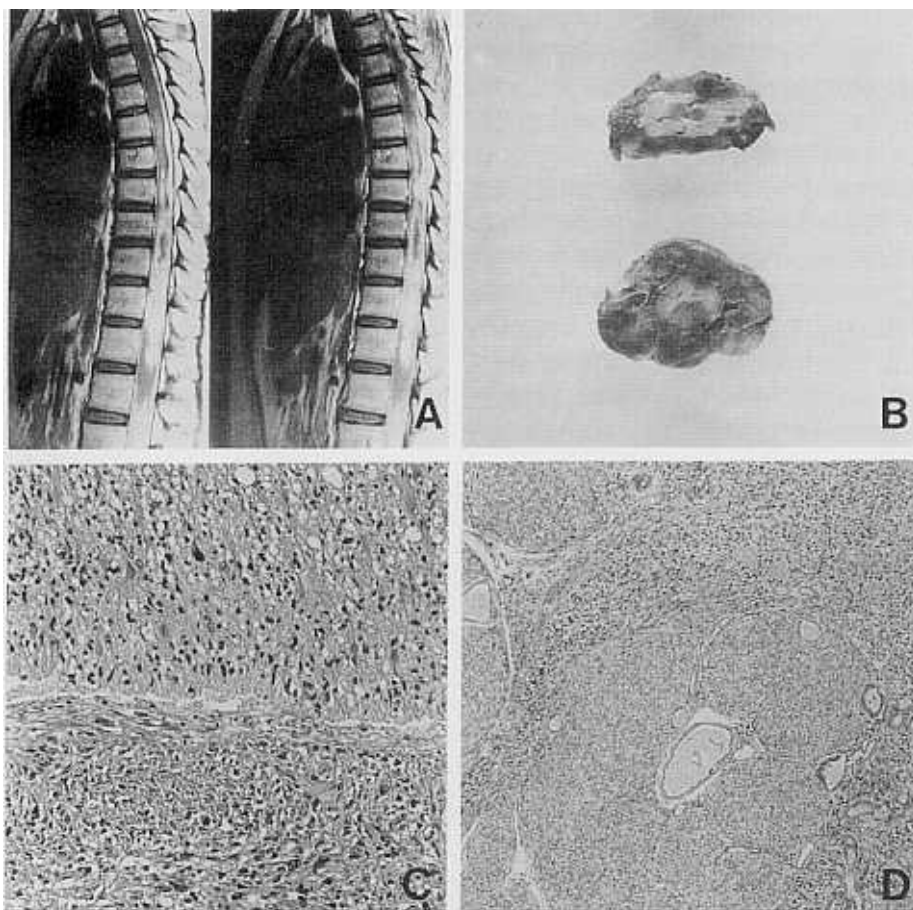


Fig. 1. Initial magnetic resonance imaging study demonstrated a diffuse irregular enhancing mass in leptomeningeal space (A). Transverse sections of the spinal cord showed an extensive leptomeningeal thickening and preserved cord contour (B) corresponding to the microscopic findings (C, D). H & E, $\times 200$ and $\times 40$.

rosensory evoked potential were within normal range, but the posterior tibial nerve somatosensory evoked potential showed conduction defects in the bilateral somatosensory evoked potential pathways. The magnetic resonance imaging (MRI) study of the T-spine showed diffuse high signal intensities from T9 to T12 of the spinal cords on a T2 sagittal image, and diffuse cord bulging at T1WI (Fig. 1A). The brain MRI was normal. In spite of large doses of steroid therapy (20 mg/kg/day) for 10 days, the symptoms slowly progressed. Symptoms of left 3rd, 4th, and 6th cranial nerve dysfunction (limitation of eyeball movements in all directions) were found on the 19th hospital day. Follow up brain MRI showed a thickening of the left cavernous sinus and carotid artery wall, and displacement of the left carotid artery to the anteromedial side (Fig. 2A). Although the patient had no medication for two weeks after self-discharge, eyeball movement progressively improved. However, weakness of the lower extremities and sensory deficits remained. One week before readmission, left vision became blurred and two days later right visual acuity also declined. She lost her bilateral eyesight for 3 to

4 days.

The patient was readmitted to the hospital because of progressive quadriplegia, paresthesia below the T5 level, visual loss of both eyes, posterior headache, neck stiffness and mild fever. She had severe neck stiffness and urinary incontinence. Often she had complained of visual and auditory hallucinations. Upon neurologic examination, the patient was alert and showed an appropriate verbal response to questions. Dilated pupils without direct and indirect light reflexes were found in both eyes. The patient neither noticed hand movement nor light perception. During left lateral gaze, a limitation of eyeball movement of the left eye was observed. Other eyeball movements were relatively intact. Motor power was 3/5 in the upper extremities; the lower extremities were paralyzed and flaccid. There was marked dysesthesia below the level of T5 upon testing for pin prick sensation, temperature sensation, vibration, and joint position. The deep tendon reflexes were + in the upper extremities and absent in the lower extremities; bilateral Babinski signs were not noted. The symptoms rapidly progressed and on the 3rd hospital day,

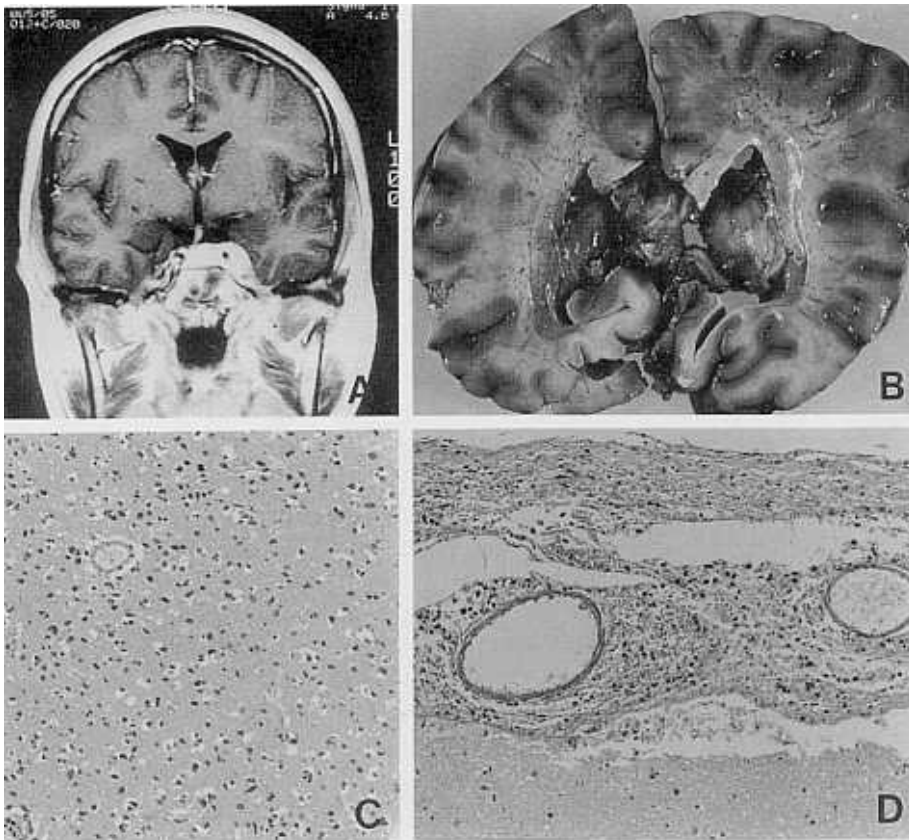


Fig. 2. Brain MRI showed an enhancing lesion in the left cavernous sinus without cerebral parenchymal mass lesion (A). Coronal sections of the brain revealed an irregular ventricular surface. Note the normal cerebral contour without gross abnormality in the hemispheres (B). Microscopic photographs show a gliomatous area involving temporal lobe (C), H & E, $\times 200$ and subarachnoidal extension (D). H & E, $\times 100$.

she complained of dyspnea. Measures to keep open the airway and ICU care were accomplished.

The results of the second lumbar puncture are also presented in the Table 1. The C- and T-spine MRI showed the spinal lesion to be more aggravated and showed diffuse or ring enhancement patterns on the sagittal and axial images. Irregular enhancement patterns involving intra- and extra-medullary portions were found on the axial image. Intracranial extension to the cisterna magna and prepontine cistern was also found. The brain CT revealed a cavernous sinus lesion and extension of the disease to the dura mater of the parietal lobe and other lobes of the brain. The patient expired on the 11th hospital day and a limited autopsy was done.

The brain, the thoracic and lumbar spinal cords, upper lobe of right lung, and the liver were examined. The liver showed a yellow subcapsular nodule (1.2 × 1 cm) in the right lobe. Microscopically examined, it was found to be focal nodular hyperplasia. The upper lobe of the right lung demonstrated bronchopneumonia. The brain weighed 1,350 gm, and cerebral configuration was normal. The leptomeninges was thin and transparent. The midbrain, pons, and medulla were unremarkable. The cerebellum was slightly swollen. Routine serial sections of the cerebrum showed slight enlargement of the lateral ventricles, which contained soft friable and redundant choroid plexuses (Fig. 2B). There were no notable abnormalities in the cerebral cortex. The cut surfaces of the cerebellar hemispheres revealed white matter softening and expansion with leptomeningeal thickening. The spinal cord was adhered to the meninges and diffusely enlarged without localized mass lesion. The cut surfaces of the thoracic cord showed extensive parenchymal and subarachnoidal involvement by a gray-white soft tumorous lesion with preservation of the anatomic contour (Fig. 1B). The lumbar cord itself was nearly normal in size, but the cauda equina was enlarged by a marked leptomeningeal widening. Microscopically, the lesion was a diffuse gliomatosis primarily involving the thoracic and lumbar spinal cords with an extensive leptomeningeal extension (Fig. 1C and D) and focally involving the parietal, temporal, and occipital lobes as well as the subarachnoidal spaces (Fig. 2C and D) and cerebellar leptomeninges. The meninges and nerve sheaths around the 3rd, and 4th cranial nerves were thickened and infiltrated by tumor cells. The spinal cord was

infiltrated by anaplastic neoplastic cells with minimal destruction of the thoracic cord parenchyma. The tumor cells revealed a high PCNA labeling index (21.3%), a high proliferative index (29.2%) and aneuploidy by flow cytometric analysis corresponding to high grade astrocytoma.^{5,6} The neoplastic cells were positive for GFAP but negative for the S-100 protein on an immunohistochemical study.

DISCUSSION

The term gliomatosis cerebri was first used by Nevin in 1938,⁷ who reported three cases with diffuse neuroglial overgrowth throughout wide areas of the brain. The definition is a diffuse infiltrating glioma involving the supratentorial compartment, posterior fossa, or even intraspinal parenchyma, sometimes in continuity. Sizable infiltrating neoplasms that also possess a solid, often necrotic core are not included in the gliomatosis category.

The clinical signs and symptoms of gliomatosis cerebri can mimic various neurologic and psychiatric problems,²⁻⁴ and depend on which part of the nervous system is involved. In neuroradiologic studies of almost all cases, there was no diagnostic finding except for a narrowing of the ventricular system observed by Bebin and Tytus.⁸ Therefore, a clinical diagnosis cannot be made before pathological examination and postmortem autopsy. In this case, magnetic resonance imaging (MRI) of the spine showed diffuse high signal intensities and diffuse cord bulgings at T1WI, suggesting an inflammatory condition such as transverse myelitis. In spite of the large doses of the steroid therapy, the neurologic symptoms progressed. The laboratory findings including peripheral blood studies, lumbar puncture and tests for viral and parasitic etiologies contraindicated infectious disease as the cause. According to the patient's clinical course and changes in the radiologic findings, the following interpretation may be possible: A tumorous growth initially involved the low thoracic spine and extended up to the cerebellum, brain stem and cerebrum by leptomeningeal and subarachnoidal spread. The high proliferating index and aneuploidy in the spinal lesion could also responsible for the rapid fatal clinical course.

Diffuse cerebrospinal gliomatosis must be clinically differentiated from encephalomyelitis and amyotro-

phic lateral sclerosis, and from primary diffuse leptomeningeal gliomatosis and dissemination of malignant glioma in a pathologic aspect. Matsushima et al. reported a case of diffuse cerebrospinal gliomatosis mimicking amyotrophic lateral sclerosis (ALS),³ The suggestive findings of ALS are weakness of the lower extremities with severe muscular atrophy, late bulbar palsy and equivocal sensory disturbance. A pathologic examination shows diffuse cerebrospinal gliomatosis predominantly involving the spinal cord and brain stem. In encephalomyelitis, particularly in acute disseminated encephalomyelitis (ADEM),⁹ the CSF protein level is moderately elevated with lymphocytic pleocytosis, generally 200 cells or less per microliter; this occurs in 80% percent of cases. It should be distinguished from diffuse infiltrative astrocytic neoplasms such as glioblastoma multiforme. Both are the consequence of marked infiltration by neoplastic glia. However, a reasonable definition stipulates that gliomatosis is a diffuse, variably differentiated neoplasm without a bulky necrotic tumorous mass. Primary leptomeningeal gliomatosis is rare and believed to originate from heterotopic glial cells.¹⁰ The diagnosis of primary leptomeningeal gliomatosis can be established only in cases in which gliomatous tissue is present in the leptomeninges without infiltration of the cerebral parenchyma.¹¹ Even though the present case is unique in that it largely involved the spinal cord, it should be considered as a spectrum of diffuse cerebrospinal gliomatosis, a third type of gliomatosis cerebri added by Moore.¹

There have been controversial interpretations concerning the pathogenesis of gliomatosis cerebri. Nevin considered the disease to be a widespread dysgenetic abnormality of a blastomatous malformation transforming to neoplastic cells.⁷ Einarson and Neel considered gliomatosis cerebri as a subgroup of a blastomatous type of cerebral sclerosis.¹² Elvidge et al. described the lesion as astrocytoma diffusum denoting an astrocytoma with extraordinary widespread extension.¹³ In the present case, the diffuse parenchymal involvement and spreading along the leptomeninges may suggest the malignant transformation of pre-existing dysgenetic glial cells on congenital basis.

There are difficulties and pitfalls in the antemortem diagnosis of this condition. Although this lesion is not curable, an early diagnosis is also important for symptom control and even improving prognosis by

appropriate treatments, such as radiotherapy and intrathecal chemotherapy.

In conclusion, cerebrospinal gliomatosis should be considered if we meet a patient whose clinical findings are imitated by a rapidly progressive diffuse cerebrospinal lesion. We recommend an adequate biopsy on the basis of clinical and neuroradiologic examination.

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