Primary Leptomeningeal Glioblastomatosis Detected in Cerebrospinal Fluid Cytology

A Case Report

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Primary leptomeningeal glioblastomatosis is a rare and fatal tumor of the central nervous system, the condition is characterized by diffuse infiltration of the tumor in the meninges without evidence of primary tumor within the brain or spinal cord. We reported an unusual case of leptomeningeal glioblastomatosis, which was detected by the consecutive cerebrospinal fluid (CSF) cytology with application of immunohistochemistry, in addition to its cytologic findings. A healthy 21 year old man, who was enlisted in the army, presented with a stuporous mental state and diffuse enhancement of meninges without evidence of primary mass lesion in the brain and spinal cord on magnetic resonance imaging (MRI). CSF cytology showed small loose clusters of tumor cells with single cells and lymphocytes. The tumor showed variable pleomorphism with coarse chromatin, irregular nuclear membranes and multi lobated nuclei. On immunohistochemical staining, the tumor cells were found to be positive for GFAP. In conjunction with radiologic findings, brain biopsy confirmed the diagnosis of leptomeningeal glioblastomatosis. The use of immunohistochemistry is helpful in confirming CSF cytologic diagnosis in patients with primary leptomeningeal glioblastomatosis.

Key words: Cerebrospinal fluid, Cytology, Glioblastoma, Immunohistochemistry, Leptomeninges
INTRODUCTION

The cytologic examination of cerebrospinal fluid (CSF) is a useful diagnostic procedure in the evaluation of patients with neurologic disorders. When a tumor involves the leptomeninges or the ventricles, the malignant cells are identified in the CSF. Leptomeningeal manifestations of glioblastoma occasionally occur in patients in the terminal stage, usually as a consequence of recurrence. However, primary leptomeningeal involvement without parenchymal lesions of the central nervous system (CNS) is very rare, only small number of reports of primary leptomeningeal gliomatosis have been published in preceding literature. The most common neoplasms encountered in CSF cytology are those of metastatic epithelial, melanomatous, and hematopoietic origins, whereas primary CNS tumors are less commonly observed in CSF cytology. We report a case of primary glioblastomatosis, exclusively involving the leptomeninges without parenchymal lesion, as detected in consecutive CSF cytology specimens.

CASE

Clinical Presentation

A healthy 21 year old man, who was enlisted in the army, was admitted to the National Army Hospital with gradual onset of a stuporous mental state for 5 days. Magnetic resonance imaging (MRI) of the brain performed upon admission showed diffuse enhancement of the leptomeninges without any evidence of parenchymal lesions (Fig. 1). The patient was transferred to Hanyang University Hospital for further evaluation and treatment. CSF examination showed an elevated protein content of 879 mg/dl and a leukocyte count of 20 per mm³ with a raised pressure. The results of CSF Gram stain, India ink preparation, KOH mount, and cryptococcal antigen tests were all negative. Bacterial, mycobacterial, fungal, and enteroviral cultures were all negative. Polymerase chain reaction for tuberculosis was negative. Specific antibodies for Borrelia burgdorferi, Mycoplasma, Leptospira, Hantaa virus, and HIV were not detected in the serum or CSF. Clinically and radiologically, meningitis or leptomeningeal carcinomatosis was suspected, but no evidence of infection and other primary malignancies was found in the CSF and imaging studies. The preliminary clinical impression was meningitis due to an unusual organism. However, the CSF cytologic findings, which were reported as ‘suspicious for malignancy’, did not allow the exclusion of possibility of primary CNS tumor. Blind open biopsy was recommended, but the patient was transferred to another hospital four months after admission. Diffuse meningeal thickening without the presence of a parenchymal mass was noted in an MRI study conducted at that hospital. The patient then underwent craniotomy for biopsy confirmation. The patient expired six months after the onset of symptoms.

Cytologic Findings

Six out of seven consecutive CSF cytology smears showed hypocellular smears of atypical tumor cells and some lymphocytes in a clean background. The tumor cells were individually scattered and occasionally formed small loose clusters with occasional rosette like arrangement. The nuclei were hyperchromatic and mildly
pleomorphic with irregular nuclear membranes, coarse chromatin and inconspicuous nucleoli. The nuclei were frequently multi-lobated, and seen nuclear molding was occasionally observed. The characteristics of the cytoplasm varied, but it was usually observed to have sparse and pale cyanophilic features (Fig. 2A-D). The tumor cells were negative for special staining for mucin or glycogen. On immunohistochemical staining, these tumor cells tested positive for GFAP (Fig. 3) and tested negative for LCA, CD3, L26, cytokeratin, NSE, CD99, p53, and Ki-67.

**Histologic Findings**

The brain biopsy from another hospital was composed of several pieces of tumor without normal cerebral

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**Fig. 2.** Representative photographs of atypical cells in CSF. (A) CSF cytology reveals rare atypical cells and some lymphocytes in clean background. (B) The tumor cells are individually scattered and occasionally form small loose clusters and rosette like arrangement. (C & D) The nuclei are hyperchromatic and mildly pleomorphic with irregular nuclear membranes, coarse chromatin and inconspicuous nucleoli. The nuclei are frequently multi-lobated (C) and occasionally show nuclear molding (D). The cytoplasm is scanty and pale cyanophilic. (Papanicolaou)

**Fig. 3.** Immunocytochemical findings. The cytoplasm of tumor cells are positive for GFAP.
Fig. 4. Histologic findings. The brain biopsy reveals typical features of glioblastoma with geographic necrosis.

parenchyma or meninges. The tumor showed typical features of glioblastoma. The tumor was hypercellular and consisted of variably pleomorphic cells in the fibrillary background. Endothelial proliferation and typical geographic necrosis with palisading of tumor cells around the necrotic area were evident (Fig. 4). On immunohistochemistry for GFAP, the tumor cells were diffusely positive in their cytoplasm. In conjunction with radiologic findings, which represented diffuse leptomeningeal enhancement without evidence of a parenchymal mass, the final diagnosis was primary leptomeningeal glioblastomatosis.

**DISCUSSION**

Primary leptomeningeal glioblastomatosis is a rare and fatal tumor of the CNS, and is characterized by diffuse infiltration of a tumor in the meninges without evidence of primary tumor within the brain or spinal cord. Primary leptomeningeal gliomatosis has a shorter clinical course and poorer prognosis than a solitary parenchymal tumor. Early diagnosis and aggressive treatment are necessary. However, diagnosis of primary leptomeningeal glioblastomatosis is often delayed because of its atypical presentation. Clinically and radiologically, diffuse leptomeningeal involvement and CSF findings tend to resemble those of meningitis rather than neoplasm. In the present case, three MRI studies were performed during a six-month period. The degree of diffuse leptomeningeal enhancement gradually increased, and it was constantly observed without any parenchymal lesions apparent in the brain or spinal cord. The clinical impression was meningitis or leptomeningeal carcinomatosis. Therefore, the patient underwent extensive bacteriologic, serologic, and cytologic examinations and was treated with empirical antibiotics, anti-tuberculous, and anti-fungal agents.

The sensitivity of CSF cytology in patients with CNS tumors is very low, but in cases of leptomeningeal involvement, malignant cells are often readily identifiable in the CSF. Glass et al. reported that only one of 66 cases was positive for CNS tumor without leptomeningeal involvement and 22 of 36 cases were positive for CNS tumor with leptomeningeal involvement. On the other hand, 8 of 15 cases showed positive cytology in cases with leptomeningeal involvement alone. These results indicated that positive CSF cytology is a reliable indicator of CNS malignancy and almost always indicates a leptomeningeal tumor. In contrast, Dietrich et al. reported only 1 of 8 cases of primary leptomeningeal gliomatosis showing atypical cells on CSF cytology. Further more, the cytologic findings have not been well described in the preceding literature. In our case, the patient had very high CSF pressure and lumbar puncture with continuous drainage was performed. CSF cytology specimens were obtained from the CSF drainage. We applied immunohistochemistry for variable antibodies in order to differentiate the type of tumor present such as malignant lymphoma, metastatic carcinoma, small round cell malignancy, or glial tumor, on the cytology smear. The cytoplasm of tumor cells was negative for LCA, cytokeratin, NSE, and CD99, but was found positive for GFAP. Due to the limited number of atypical cells in CSF specimens used for immunohistochemistry cytologic findings were not sufficient enough to make a diagnosis. However, the possibility of a CNS tumor remained, and a brain biopsy was recommended for confirmation at that time.

The differential diagnosis of atypical cells in the CSF cytology include both metastatic and primary CNS
tumors. The most common metastatic tumors are carcinomas of the lung and breast, malignant melanoma, and lymphoma.15 Good clinical history and immunohistochemical stains, including cytokeratin subtypes, TTF-1, CEA, LCA, HMB 45, are useful in characterizing malignant cells of unknown origin. The most common primary CNS tumors are the astrocytic neoplasms, followed by medulloblastoma and ependymoma.15 CSF cytology of astrocytomas shows single large hyperchromatic cells or clusters. The amount of hyperchromasia and pleomorphism of the cells depends on the grade of the glial tumor. Fine cytoplasmic extension may be seen in the tumor of glial origin. CSF cytology of ependymoma shows cellular smear, and the neoplastic single cells and loose clusters consist of cuboidal to low columnar cells with round uniform nuclei and moderate amount of cytoplasm. Cytologic specimen of medulloblastoma is cellular with single cells and clusters, consisting of slightly large cells with nuclear molding and scant cytoplasm. Rosette formation and individual cell necrosis may be seen.

We reported an unusual case of leptomeningeal glioblastomatosis, which was detected on the consecutive CSF cytology with application of immunohistochemistry, in addition to its cytologic findings. Multiple lumbar punctures with use of immunohistochemistry on cytology smears may improve the sensitivity of CSF cytology in the patients with primary or metastatic CNS tumors.

REFERENCES