Recurrent Malignant Histiocytosis with Cerebrospinal Involvement
—Case Report—

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Abstract

A 61-year-old male presented with recurrent malignant histiocytosis of the brain manifesting as nausea and headache. Malignant histiocytosis is a disorder of proliferating histiocytes characterized by a rapidly progressive and fatal course, but central nervous system involvement is relatively rare. Magnetic resonance (MR) imaging demonstrated cerebrospinal fluid (CSF) dissemination of histiocytes as a low-intensity area on the T₁-weighted image with marked gadolinium-diethylenetriaminepenta-acetic acid enhancement and a high-intensity area on the T₂-weighted image. CSF cytological examination revealed an increased level of atypical histiocytes. Brain and spine irradiation, and intrathecal methotrexate and prednisolone administration induced remission. MR imaging is particularly useful for the diagnosis of meningeal dissemination of malignant histiocytosis.

Key words: malignant histiocytosis, cerebrospinal involvement, magnetic resonance imaging

Introduction

Malignant histiocytosis is a disorder involving systemic, progressive invasion of morphologically atypical histiocytes and their precursors.¹² The clinical features of malignant histiocytosis include fever, wasting, lymphadenopathy, hepatosplenomegaly, anemia, and pancytopenia. The disease is usually fatal, with death occurring a few weeks to a few months after diagnosis. The age of patients ranges widely from 2 months to 79 years.⁷,¹⁰,¹⁴ Nervous system involvement is uncommon but well described, usually presenting as dural and leptomeningeal infiltration on postmortem examination.²,³,⁸,⁹ However, computed tomographic (CT) scanning is seldom reported, and there are no reports of magnetic resonance (MR) imaging.¹⁴ We report a patient with recurrent malignant histiocytosis manifesting as meningeal dissemination diagnosed by MR imaging and cytological examination of the cerebrospinal fluid (CSF).

Case Report

A 61-year-old male was admitted to our hospital in May, 1987, complaining of persistent fever and fatigability. Hematological examination revealed severe pancytopenia and the presence of abnormal cells in the bone marrow, which were considered to originate from the mononuclear phagocytic system. The lactate dehydrogenase level was remarkably increased and there was no lymphadenopathy. The diagnosis was malignant histiocytosis. He was treated by combination chemotherapy which achieved complete remission, and was followed in our outpatient clinic.

He returned to our hospital in December, 1989, complaining of nausea and headache on sleeping. He had mild anemia, but no fever or abdominal pain. Neurological examination showed incomplete left abducens nerve paresis and nuchal stiffness. Skeletal x-ray examination found no abnormalities. Precontrast CT showed a faint low-density area around the
left trigone. Postcontrast CT showed markedly enhanced lesions in the bilateral trigones, but the low-density area was not enhanced (Fig. 1). MR imaging revealed a low-intensity area on the T1-weighted image and a high-intensity area on the T2-weighted image around the left trigone. MR imaging with gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) showed marked enhancement of the masses in the trigones, and the walls of the bilateral ventricles were also enhanced (Fig. 2). This wall enhancement suggested CSF dissemination extending to the third and fourth ventricles.

The CSF was light yellowish and highly turbid. The protein level was 720 mg/dl (normal 10-45 mg/dl) and the glucose level was 9 mg/dl (normal 40-70 mg/dl). CSF cytological examination revealed an increased number of histiocytes which were large, pleomorphic, and had atypical features. The nuclei were large with fine to coarse chromatin and the cytoplasm was abundant and vacuolated. Erythrophagocytosis was not observed. These features were similar to those of the bone marrow specimen at the first admission (Fig. 3).

He was treated with radiotherapy (whole brain 40 Gy, whole spine 20 Gy) and chemotherapy (intrathecal methotrexate and prednisolone administration). Headache, nausea, and diplopia improved a few days after radiotherapy. The dissemination along the ventricular wall on the MR images also disappeared after irradiation. CSF cytological ex-

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**Fig. 1** *left:* Precontrast CT scan, demonstrating a faint low-density area around the left trigone. *right:* Postcontrast CT scan, demonstrating markedly enhanced lesions in the bilateral trigones.

**Fig. 2** *left:* T1-weighted MR image, demonstrating a low-intensity area around the left trigone. *center:* T2-weighted MR image, demonstrating a high-intensity area around the left trigone. *right:* T1-weighted MR image with Gd-DTPA, showing marked enhancement of the masses in the bilateral trigones and ventricular walls.

**Fig. 3** Photomicrograph of the CSF specimen, showing an increased number of histiocytes which were large, pleomorphic, and had atypical features. The nuclei were large with fine to coarse chromatin and the cytoplasm was abundant and vacuolated. HE stain, ×400.
amination showed a reduction in malignant cells, and the CSF protein and glucose levels had normalized. He was discharged after 2 months.

Discussion

Histiocytosis or reticulosis is a pathological condition characterized by the systemic proliferation of histiocytes or reticuloendothelial cells. Neoplastic and inflammatory processes are difficult to differentiate, because histological examination shows benign features even in malignant cases. Solitary or multiple lesions of the skull are known as eosinophilic granuloma or part of the Hand-Schuller-Christian syndrome, respectively, while extensive involvement of soft tissue characterizes the entity of Letterer-Siwe disease. In 1953, Lichtenstein proposed that these three entities were parts of a disease spectrum termed "histiocytosis X." Malignant histiocytosis, characterized histologically by widespread tissue infiltration of histiocytic cells, was originally described as "histiocytic medullary reticulosis" and the term "malignant histiocytosis" was introduced in 1966. However, the condition has subsequently been denoted by a multitude of names. The relationship of each disease, as well as other disorders of proliferating histiocytes, awaits elucidation by evolving concepts of pathogenesis and nosology.

Bone marrow aspirates and biopsies from involved tissues (liver, lymph node, spleen, and skin) are the best means for establishing the diagnosis. Positive findings in the CSF are rare, but malignant histiocytosis has been diagnosed from a lumbar puncture. Previously, malignant histiocytosis was considered rare with an invariably fatal outcome in weeks or months after diagnosis. Recently, early diagnosis and treatment including corticosteroids, cyclophosphamide, vincristine, procarbazine, 6-mercaptopurine, methotrexate, daunomycin, cytosine arabinoside, azathioprine, and nitrogen mustard have produced a good response. In our patient, the diagnosis of malignant histiocytosis on the first admission was based on the detailed findings in the bone marrow. He was successfully treated by combination chemotherapy. However, he later developed headache and nausea. We suspected CSF involvement of malignant cells based on the CT and MR imaging, while the diagnosis of recurrent malignant histiocytosis was based on the CSF cytology. MR imaging was superior to CT, probably because MR is more sensitive to tissue water content and suffers no degradation due to the tissue-bone interface. Both postcontrast CT and Gd-DTPA-MR imaging are very effective for identification of blood-brain-barrier breakdown. The Gd-DTPA-MR technique is superior for investigation of inflammatory disease due to the absence of tissue-bone interface obscuration, and can detect faint brain edema and leptomeningeal dissemination of progressive and invasive malignant diseases like malignant histiocytosis.

Malignant histiocytosis was thought to be a progressive and rapidly fatal disease, although often responding to therapy. However, several recent cases have shown extended survival periods. Some of these cases showed evidence of central nervous system (CNS) involvement at a relatively early stage. Therefore, some form of CNS prophylaxis might be necessary in the treatment of malignant histiocytosis. The CSF cytological study was an important part of the diagnosis in our case. However, repeated CSF examinations are invasive, while malignant cells were only detected in the CSF of patients with neurological symptoms. MR imaging is not invasive, and successfully indicated malignant histiocytosis in our patient. Monitoring of neurological symptoms and periodic MR imaging are quite useful for the early diagnosis of recurrent malignant histiocytosis in the CNS, even in patients who have previously achieved complete remission.

References

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