Central nervous system malignant lymphoma presenting with central neurogenic hyperventilation

--a case report and review of the literature--

Yasushi Shibata, M.D., Kotoo Meguro, M.D.,F.R.C.S.C.,
Kiyoshi Narushima, M.D., Fumiho Shibuya, M.D.,
Mikio Doi, M.D., Youichi Kikuchi, M.D.

Department of Neurosurgery,
Pathology and Radiology,
Tsukuba medical center hospital,
Tsukuba, Ibaraki, 305, Japan

Running Title: Central nervous system malignant....

Address for correspondence:

C/O Kotoo Meguro, M.D.,F.R.C.S.C.

Yasushi Shibata, M.D.

Department of Neurosurgery

Tsukuba medical center hospital

Tsukuba, Ibaraki 305, Japan

Telephone: 0298-51-3511

Abstract

We describe 72-year-old female who presented with progressive right hemiparesis and central neurogenic hyperventilation. Pathological and radiological study revealed diffuse infiltration of malignant lymphoma. We reviewed 12 cases of tumor induced central neurogenic hyperventilation, and discussed the pathophysiology of central neurogenic hyperventilation and the limit of radiological study as a diagnostic modality.

Key words: Central Nervous System

Hyperventilation

Lymphoma

Magnetic Resonance Imaging

Introduction

Central neurogenic hyperventilation is one of the neurological symptoms commonly seen in the comatous patients who have gross intracranial lesions. However, it is quite rare to see central neurogenic hyperventilation in the awake patients. We recently experineced a case of the tumor induced central neurogenic hyperventilation in the awake patient. The autopsy of the central nervous system revealed diffuse infiltration of malignant lymphoma. We reviewed the literature of cases of tumor induced central neurogenic hyperventilation, and discussed the pathophysiology of hyperventilation.

Case report

A 72-year-old female was initially seen by a family doctor on January 17, 1990 complaining with right lower extremity weakness since December 1989. Computed tomographic(CT) scan showed no abnormal finding. However her right hemiparesis made progress to the right upper extremity, so she reffered to our hospital in January 22. 1990. Physical examination showed no abnormal findings without abnormal respiratory pattern. Neurological examination showed right hemiparesis and hypesthesia, general hyperreflexia and urinary incontinence, but her conciousness was alert. Brain CT scan disclosed multiple low density area in the bilateral white matter(Fig.1), but cerebral angiography showed almost normal findings. The initial diagnosis was multiple cerebral infarction, but the intravenous infusion of the low molecular weighted dextran and urokinase had no effect. Since the beginning of February 1990, she started fast and deep respiration and the hyperventilation persisted during sleep. Arterial blood gas analysis under the condition of room air revealed pH 7.613, pCO2 17.4, pO2 100, indicating the presence of hypocapnea, slight

hyperoxycemia and marked respiratory alkalosis. We investigated the cause of hyperventilation. Chest rentgenography and echocardiography revealed no pathology such as pulmonary fibrosis, congestive heart failure or pulmonary embolism. Lumbar cerebrospinal fluid(CSF) revealed mild pleocytosis with lymphocyte dominancy and slightly elevated level of protein. The cytology study of CSF revealed no abnormality. And other laboratory data and cerebral angiography were negative for autoimmune disease or cerebral vasculitis. Follow up brain CT on March 6, disclosed the increase of left parietal low density area(Fig.1). Brain stem magnetic resonance imaging(MRI) disclosed no abnormality except for possible long T2 lesion in the pons. Both enhanced CT and MRI of the patient on April disclosed well enhanced lesions at bilateral paraventricular white matter which extended into corpus callosum and the left-sided enhanced lesion extending to the pons along the corticospinal tract(Fig.2,3,4). We scheduled biopsy of the lesion but the patient expired because of severe pneumonia on April 15. 1990. The autopsy of only brain was

permitted. Macroscopically the area of discoloration was obvious in the white matter and brain stem, corresponding to the lesion delineated by MRI. MRI study of the Formaldehyde-fixed brain specimen showed almost same appearance with in vivo MRI study in April(Fig.5). Histologically tumor cell was infiltrated diffusely around perivascular space(Fig.6). Immunohistological staining revealed B cell lymphoma around perivascular space and abundance of reactive T cell lymphocyte(Fig.7). The tumor cell infiltrated along the vessel and tract, especially left corticospinal tract down to the upper cervical spinal cord. The infiltration of the tumor cell was also found in the entire central nervous system exceeding the area of Gadolinium enhanced lesion in the MRI. In the pons, the tegmentum was widely infiltrated by tumor cells without causing mass effect in addition to the tumor nodule in the basis pontis.

Discussion

Central neurogenic hyperventilation in the strict sense is extremely rare neurological manifestation. Plum and Swanson reported 9 cases of central neurogenic hyperventilation with brainstem infarction(10). Complete autopsy of 6 cases showed necrosis of central portion of pons in five cases and compression of pons in one. The common lesion of all 6 cases is the infarction of medial pontine nuclei, medial pontine reticular formation and corticospinal tract in pons. The lateral pontine reticular formation and laterally located fiber tract were spared. They proposed the hypothesis that the central neurogenic hyperventilation result from uninhibited stimulation to both inspiratory and expiratory center in medulla by lateral pontine reticular formation and by laterally located descending neural pathway. But these cases had suffered moderate to extensive bronchopneumonia or pulmonary congestion. The value of PaO2 of these patients were below the normal disproportionated to the extent of hyperventilation(8). Ngai and Wang reported the hyperventilation by the electrolysis of dorsolateral pons of cats(6). But other

author failed to produce hyperventilation in the similar experiment(10). Later Plum proposed another hypothesis that the local stimulation of chemosensitive area by hydrogen ions produced by tumor may cause central hyperventilation(9). But the Positron emission computed tomography(PET) study revealed pH of the tumor in vivo is always more alkalotic than the gray or white matter(12). And Bateman argued against local acidification of the CSF in the region of the brainstem as the mechanism of hyperventlation, because central neurogenic hyperventilation is very rare despite the relative frequency of meningeal carcinomatosis(1). The hyperventilation in the comatous patients with intracranial disorder was sometimes regarded as central neurogenic hyperventilation. Acute intracranial lesion such as hemorrhage or infarction is frequently accompanied with pulmonary complications. The increase of catecholamine and hypertension contribute to pulmonary congestion and the disturbance of consciousness may result in pneumonia. In the majority of cases, the hyperventilation with intracranial disorder seems to be

caused by pulmonary complications.

We reviewed 13 cases of tumor induced central neurogenic hyperventilation including our case(1,2,4,5,7,9,11,13,14,15,16 Table 1). The involvement of the pons was present in ten cases and absent in one. Although Bateman's case revealed no lesion below midbrain at autopsy(1), pontine lesion seems to be a responsible lesion of central neurogenic hyperventilation in most cases. Tumor infiltration in the medulla was recognized in 4 cases with the microscopic examination(2,11,16). These findings did not support the hypothesis that central neurogenic hyperventilation is caused by the uninhibited stimulation of respiratory center in intact medulla.

Among 13 cases of tumor induced hyperventilation, six were lymphoma, four were astrocytoma and three were of unknown pathology. Malignant lymphoma is rare tumor, represented fewer than 1% of primary brain tumor(3). Relative high frequency of the lymphoma among cases of tumor induced hyperventilation appeared significant. For this reason, the possibility of central nervous

system malignant lymphoma should be kept in mind in the case of central neurogenic hyperventilation.

What is the common denominator responsible for central neurogenic hyperventilation among these 13 cases? One of the common features may be diffuse infiltration of tumor cells in the pons. Lymphoma has been known to be infiltative and four cases of astrocytoma were involving entire pons. It can be postulated that to produce central neurogenic hyperventilation, the pons should be infiltrated diffusely, but should preserve its structure without major destruction. In our case, Gadolinium enhanced lesion along the pyramidal tract in the MRI scan was not sufficient to cause central neurogenic hyperventilation. However, further post-mortem microscopic examination revealed that tumor cells were found in the entire pons. Progressive cerebral atrophy demonstrated in the serial CT scan may indicate neutrial disorder caused by diffuse tumor infiltration.

Gadolinium enhanced MRI revealed wider area of the lesion than the contrast enhanced CT. So Gadolinium enhanced MRI was more acurate in determining the area of the lesion than the

contrast enhanced CT. However the limit of MRI was well illustrated by the fact that the pathological study revealed more diffuse infiltration of the tumor cell. Clinical findings such as progressive hemiparesis were well correlated with Gadolinium enhanced MRI which showed probably an area of blood brain barrier disruption. Gadolinium enhanced MRI is most usefull radiological study in delineating an area of brain edema but tumor cell without edema may not be recognized even with the Gadolinium enhanced MRI. It is known that radiotherapy or corticosteroid could improve clinical symptoms and vanish enhanced mass in CT or MRI. However one should be cautious that this disappearance of enhanced lesion dose not necessarily indicate complete elimination of the tumor cell, but the decrease of interstitial edema. Gadolinium enhanced MRI is usefull in the diagnosis of central nervous system lymphoma, but one should be aware that the area of tumor infiltration is more extensive than the area of Gadolinium enhanced lesion.

References

1. Bateman DG, Gibson GL, Hudgson P, et al: Central neurogenic hyperventilation in a concious patient with a primary cerebral lymphoma. Ann Neurol 17:402-405, 1985

2. Goulon M, Escourolle R, Augustin P, et al: Hyperventilation primitive par gliome bulbo-protuberantiel. Rev Neurol 121:636-639, 1969

3. Hochberg FH, Miller DC: Primary central nervous system lymphoma. J Neurosurg 68:835-853, 1988

4. Lange LS, Laszlo G: Cerebral tumour presenting with hyperventilation. J Neurol Neurosurg Psychiat 28:317-319, 1965

5. Nakasu Y, Nakasu S, Matsuda M, et al: Central neurogenic hyperventilation with pontine tumor. Case report and a review of the literature. Arch Jpn Chir 57:165-171, 1988

6. Ngai SH, Wang SC: Organization of central respiratory mechanisms in the brain stem of the cat: localization by stimulation and destruction. Am J Physiol 190:343-349, 1957

7. Pauzner R, Mouallem M, Sadeh M, et al: High incidence of primary cerebral lymphoma in tumor-induced central neurogenic hyperventilation. Arch Neurol 46:510-512, 1989

8. Plum F, Posner JB: The diagnosis of stupor and coma. F. A. Davis company, Philadelphia, 1980

9. Plum F: Mechanisms of "central" hyperventilation. Ann Neurol 11:636-637, 1982

10. Plum F, Swanson AG: Central neurogenic hyperventilation in man. Arch Neurol Psychiatry 81:535-549, 1959

11. Rodriguez M, Baele PL, Marsh HM, et al: Central neurogenic hyperventilation in an awake patient with brainstem astrocytoma. Ann Neurol 11:625-628, 1982

12. Rottenberg DA, Ginos JZ, Kearfott KJ, et al: In vivo measurement of brain tumor pH using {11C}dimethyloxazolidinedione and positron emission tomography. Ann Neurol 16:132-133, 1984

13. Salvesen R: Pontine tumour with central neurogenic hyperventilation. J Neurol Neurosurg Psychiatry 52:1441-1442, 1989

14. Sunderrajan EV, Passamonte PM: Lymphomatoid granulomatosis presenting as central neurogenic hyperventilation. Chest 84:634-636, 1984

15. Suzuki M, Kawakatsu T, Kamoshita S, et al: A case of pontine tumor associated with repeated episodes of hyperventilation and ketosis. Paedriatr Univ Tokyo 10:58-61, 1964

16. Tinaztepe B, Tinaztepe K, Yalaz K, et al: Microgliomatosis presenting as sustained hyperventilation. Turk J Pediatr 23:269-275, 1981

Legend of figures

Fig.1 CT scan on January 22 and March 6, 1990.

Showing multiple low density area in the bilateral white matter and enlargement of left parietal low density area. Note that cerebral atrophy became prominent in the CT scan on March 6.

Fig.2 CT scan with contrast enhancement on April 6, 1990.

Showing well enhanced, multiple lesions in the bilateral paraventricular white matter with infiltration to the corpus callosum and the left enhanced lesion extending to the cerebral peduncle. Note that there was little edema or mass effect.

Fig.3 Axial view of T1 (TR 300 msec, TE 14 msec) and Proton (TR 2000 msec, TE 30 msec) weighted MRI on April 11, 1990.

Showing multiple both of T1 and T2 elongated lesions in the bilateral paraventricular white matter and left pons with little edema and mass effect.

Fig.4 Gadolinium-DTPA enhanced T1 (TR 300 msec, TE 14 msec)

weighted axial and coronal MRI in April 11, 1990.

Showing well enhanced lesions in the bilateral paraventricular white matter with the involvement of the corpus callosum and the left enhanced lesion extending into the pons with small edema and mass effect.

Fig.5 Coronal view of Proton (TE 2000 msec, TR 30 msec) and T2 (TR 2000 msec, TE 80 msec) weighted MRI of the Formaldehyde-fixed brain specimen of the case.

Showing T2 elongated lesions in the bilateral paraventricular white matter.

Fig.6 Microscopical view of the specimen of the case with Hematoxylin-Eosin stain. Showing diffuse infiltration of malignant lymphoma cell around perivascular space. *800

Fig.7 Microscopical view of the specimen of the case with immunohistological stain (left: L-26, right: UCHL-1).

Showing diffuse infiltration of B cell lymphoma around perivascular space and infiltration of reactive T cell lymphocyte. *200