—Report on Experiments and Clinical Cases—

A Pre-senile Case of Limbic Encephalitis and Cerebellar Degeneration, with Subacute Onset of Progressive Dementia

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Abstract

In case a pre-senile patient presented subacutely progressive dementia, secondary dementia, such as paraneoplastic neurological syndrome (PNS), hypothyroidism, confusion, early phase of primary degenerative dementia and prion diseases are to be considered. It is a case of pathologically confirmed, and clinico-pathologically assessed limbic encephalitis with cerebellar degeneration.

The patient was a 63-year old male, with a well followed up medical history of gastric cancer 8 years earlier. Four weeks after he presented himself at our hospital his memory and disorientation progressively declined. A neurological examination revealed gaze nystagmus, with potential secondary dementia. However, no abnormal findings were detected from systemic radiological examination, or from chemical analyses. Two months later, after the onset of the disease, he presented additional symptoms, including seizure, gait disturbance, and insomnia. On admission, neurological examinations revealed gaze nystagmus and progression of dementia; however, his thought process was relatively preserved. No paroxysmal synchronized discharge was seen on electroencephalogram. Chest X-rays showed an inflammatory infiltration. In spite of anti-biotic medication, he died due to respiratory failure.

The autopsy was limited to the brain. Histologically, limited lymphocytic infiltration into the hippocampus through the entorhinal cortex, with marked neuronal loss and gliosis was observed. Neuronophagia, microglial nodules, and perivascular lymphocytic infiltration were also seen. Additionally, most of the Purkinje cells in the cerebellum were lost, with Bergmann's gliosis and sparse lymphocytic infiltration. No tumor was observed in the brain. Pathological findings of the brain were compatible with paraneoplastic limbic encephalitis and cerebellar degeneration, though no neoplasm, clinically or pathologically, was detected in this patient. Consequently, it is suggested that when a senile patient presents sub-acute onset of progressive dementia, with a variety of neurological symptoms, paraneoplastic syndrome is to be taken into consideration, even if a tumor or an auto-antibody is not detected since the resection of the tumor is still the best therapeutic means. Otherwise immuno-suppressive and steroid therapies should be used.

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Introduction

When a pre-senile patient presented with subacutely progressive dementia characterized by memory disturbance and disorientation, secondary dementia, such as paraneoplastic neurological syndrome (PNS), hypothyroidism, confusion, early phase of primary degenerative dementia, and prion diseases are to be considered. We report a case of pathologically confirmed, and clinico-pathologically assessed limbic encephalitis with cerebellar degeneration.

Patient History

The patient was a 63-year old male, with a well followed up medical history of gastric cancer eight years earlier. Four weeks after he presented himself at our hospital, his memory disturbance and disorientation progressively declined. A neurological examination revealed gaze nystagmus, and potential secondary dementia. However, no abnormal findings were detected from serial brain, abdominal, and chest computed tomography, or from chemical analyses, such as vitamin B1/B12 and thyroid hormone. Serologically, no elevated viral titer was detected. Two months after the onset of the disease, the patient exhibited gait disturbance, squeal and generalized tonic/clonic seizure with EEG spikes, which is an indication of anti-convulsant medication. Additional symptoms of insomnia, otherwise squeal, required major tranquilizer medication, disturbing his daily life activities. On admission to our hospital, neurological examinations revealed gaze nystagmus, disorientation of time and place, and disturbance of memory in particular, scoring around 10 of 30 points using the Mini-Mental-State-Examination. His thought process was relatively preserved, and his conversation was not tangential. No paroxysmal synchronized discharge was seen on electroencephalogram. Chest X-ray examinations showed inflammatory infiltration on both the lower lung fields. Although anti-biotic medication was performed, he died due to respiratory failure. An autopsy was conducted, with limited permission, to the brain.

Methods

The brain was fixed for fifteen days in 10% formalin, and cut into coronal 1.0 cm thick sections. For histological examination, hematoxylin-eosin,

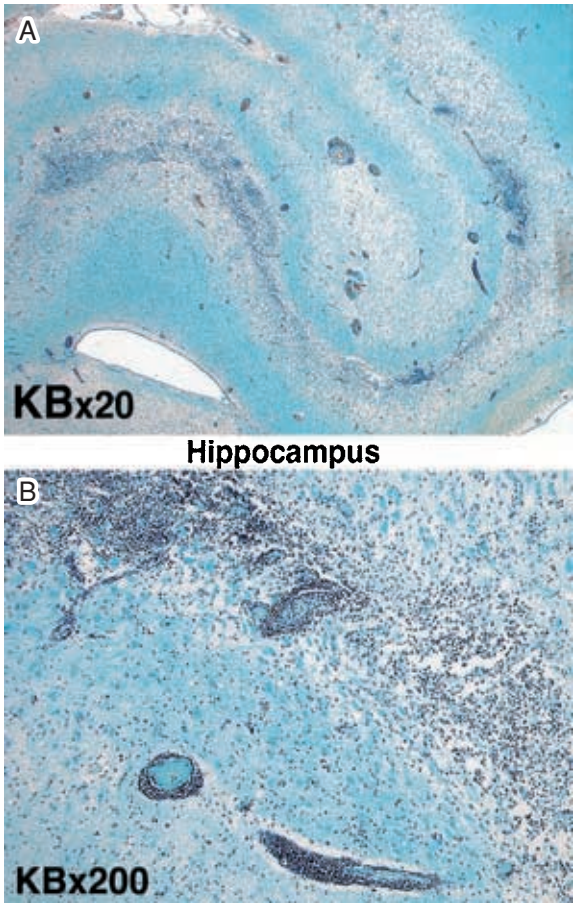

Fig. 1 **A**. Marked lymphocytic infiltration along the pyramidal neurons. **B**. High power view shows neuronal loss (right loose area) and gliosis (background). Perivascular lymphocytic cuffing is also shown (bottom).

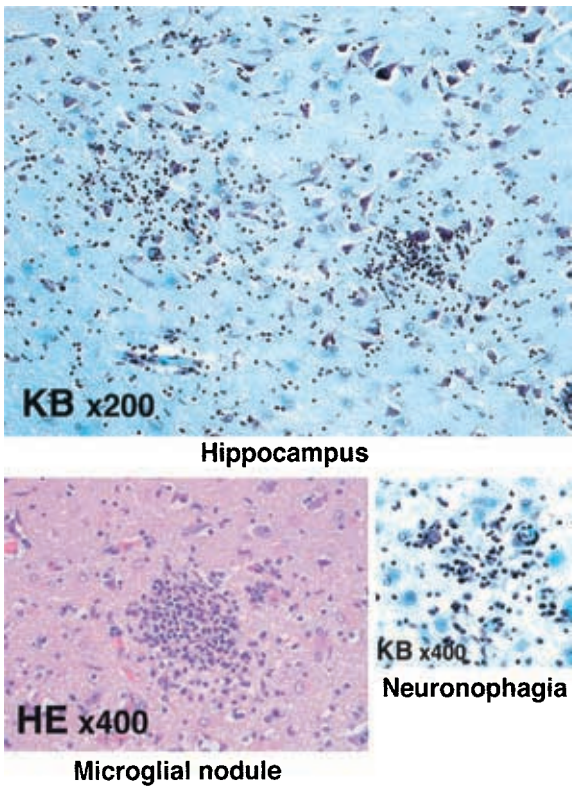

Fig. 2 Microglial nodules and neuronophagia in hippocampus, with scattered lymphocytes.

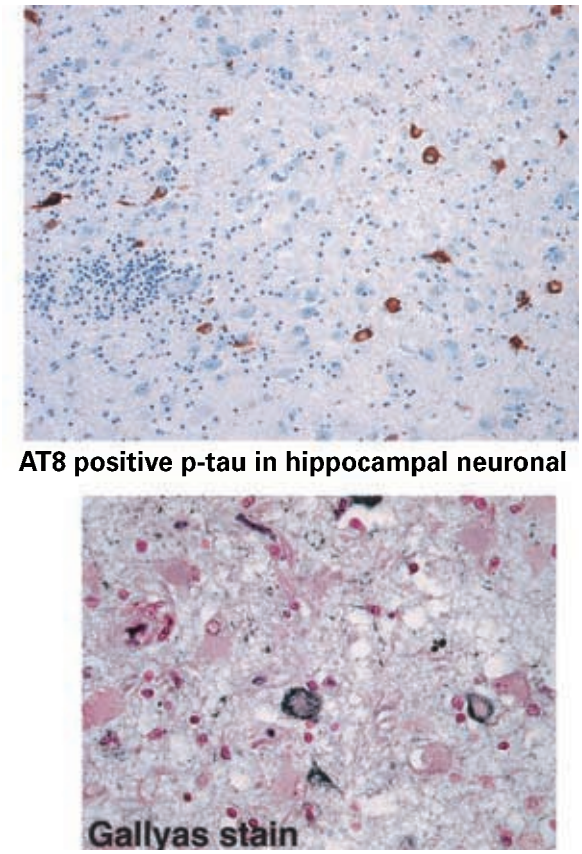

Fig. 3 Neuronal cytoplasmic neurofibrillary tangles are scattered in entorhinal cortex through hippocampus, stained brawn with DAB under anti-Tau immunohistochemical method (upper figure) and stained black with Gallyas method (lower figure).

myelin (KB staining) and, silver impregnation methods including Bodian and Gallyas staining, were routinely performed. Immunohistochemical staining for neurofibrillary tangles, senile plaques, and IgG were performed using anti-phosphorylated Tau antibody, AT8, anti-beta amyloid protein antibody, and anti-IgG antibody, using the ABC method, and were visualized with diaminobenzidine (DAB).

Pathological Findings

The brain weighed 1,280 g. Macroscopically, the brain showed mild meningeal congestion, mild atherosclerosis, and diffuse cerebral atrophy consistent with the patient's age. Histological observations showed limited lymphocytic infiltration into the hippocampus through the entorhinal cortex, with marked neuronal loss and gliosis (**Fig. 1 A and B**). Neuronophagia, microglial nodules, and perivascular lymphocytic infiltration were observed in the adjacent gray matter, amygdala, and mammillary body (**Fig. 2**). Additionally, anti-Tau immunohistochemistry revealed scattered neurofibrillary tangles limited to the entorhinal cortex through the anterior hippocampus, which is consistent with Braak's stage II-III (**Fig. 3**). No senile plaque was observed. Most of the Purkinje cells in the cerebellum were lost, with Bergmann's gliosis and sparse lymphocytic infiltration (**Fig. 4**). Subarachnoid lymphocytic infiltration was mild and limited to the medial temporal area. No neoplastic lesions were observed. Immunohistochemistry, using anti-IgG antibody, showed partial granular staining in the molecular layer of the cerebellum, suggesting some joining of the humoral immunity (**Fig. 5**).

Discussion

Paraneoplastic neurological syndrome (PNS) is characterized as a variety of sub-acutely progressive

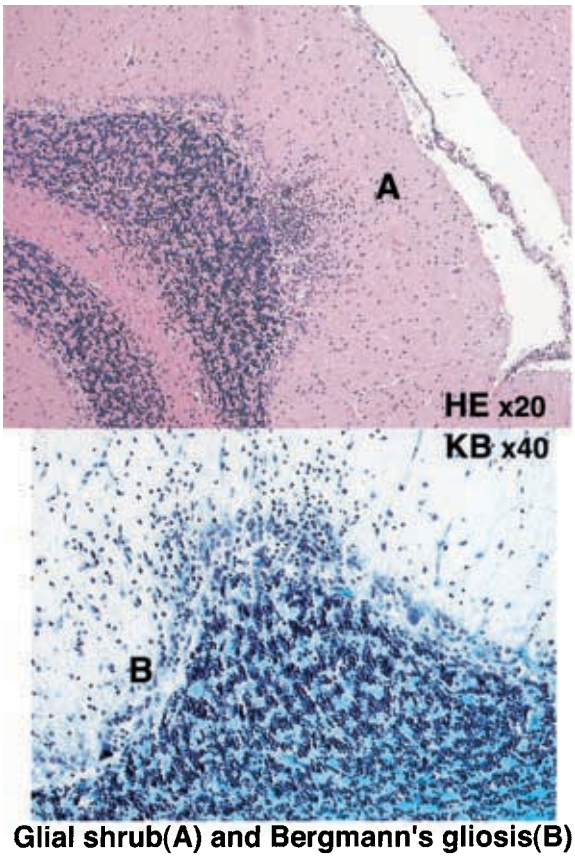

Fig. 4 Cerebellar degeneration, focused on Purkinje cells, with glial shrub (A), Perkinje cell loss and Burgmann's glosis (B).

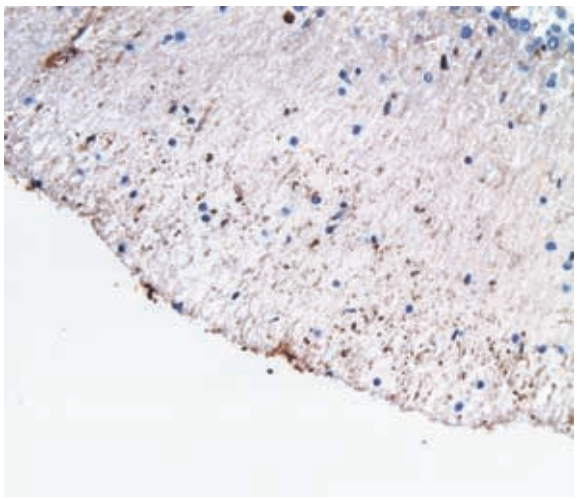

Fig. 5 Granular anti-IgG immunohistochemical staining, along dendrites of Perkinje cells in the molecular layer of cerebellum.

neurological symptoms, lacking neoplastic and metastatic lesions in the nervous system usually with a malignant neoplasm existing in another organ. In the brain of this patient, neither clinical nor pathological examination revealed metastasis nor was elevated viral titer detected. In addition, histological findings of lymphocyte-dominant encephalitis, limited to the limbic areas along with cerebellar degeneration indicated that this patient's neurological signs were consistent with PNS. However, it had been eight years since the patient received a total gastrectomy for gastric cancer, and no other neoplastic lesion was clinically detected. Since the autopsy was limited to the brain, we were unable to determine if a malignant neoplasm existed in another part of the body.

Though still under debate, the major hypothesis of the pathogenesis of paraneoplastic syndrome is auto-immunization, driving neuronal death through cytotoxic T-cells. Since 1985, dozens of auto-antibodies in patient's serum have been reported, about one auto-antibody per year[1]. Regarding limbic encephalitis and/or cerebellar degeneration, the Hu antibody in the patients with small cell carcinoma of lung, and the Yo antibody in those with ovarian or breast cancer, are most frequently detected[1]. The specificity is close to 100%. Therefore, when one of those antibodies is found, the probability of a tumor is very high. However, the sensitivity of these clinically relevant antibodies for a paraneoplastic etiology is about 50～60%[2]; therefore, the diagnosis of this syndrome is made even in the absence of one of these antibodies. Additionally, most of the primary neoplastic lesions tend to be small and limited, when many of them are found following neurological insults[3-5].

As for the present case, although no auto-antibody or tumor was detected through clinical examination, histological findings of the brain is compatible with paraneoplastic limbic encephalitis and cerebellar degeneration. From a clinico-pathological standpoint, a considerable amount of neurofibrillary tangles with neuronal loss expressed in the entorhinal cortex, should have contributed considerably to the sub-acute progression of the dementia.

Consequently, when pre-senile or senile patients present the subacute onset of progressive dementia, with a variety of neurological symptoms,

paraneoplastic neurological syndrome should be considered, and whether a neoplasm exists should be determined immediately. Resection of the tumor is still the best therapeutic means; otherwise, immuno-suppressive and steroid therapies are necessary.

References

1. Voltz R: Paraneoplastic neurological syndromes: an update on diagnosis, pathogenesis, and therapy. Lancet Neurology 2002; 5: 294–305.
2. Verschuuren M, Perquin G, Velde TA : Anti-Hu antibody titre and brain metastases before and after treatment for small cell lung cancer. J Neurol Neurosurg Psychiatry 1999; 67: 353–357.
3. Graus F, Keime-Guibert F, Rene R: Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001; 124: 1138–1148.
4. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology 1998; 50: 652–657.
5. Sillevis P, Smitt J, Grefkens B, de Leeuw: Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis / sensory neuronopathy. J Neurol 2002; 249: 745–753.

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