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AN AUTOPSY CASE OF CARCINOMA OF THE LUNG ASSOCIATED WITH SUBACUTE CEREBELLAR DEGENERATION AND EATON-LAMBERT SYNDROME

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Abstract

The following is a report of an autopsy case of rare occurrence of small cell anaplastic carcinoma of the lung associated with subacute cerebellar degeneration and Eaton-Lambert syndrome.

The patient was a 55-year-old man who developed rapidly progressive ataxia and dysarthria. Physical examination revealed carcinoma of the lung and Eaton-Lambert syndrome in addition to cerebellar symptoms and signs. At autopsy cerebellar degeneration was found to be restricted only to the paleocerebellum, different from other cases with subacute cerebellar degeneration as a remote effect of malignant neoplasms.

INTRODUCTION

Malignant neoplasms may produce various neurological symptoms and signs not only due to direct involvement of the nervous system but also due to remote effect of the malignancies[1]. The neurological condition brought about by the latter is called carcinomatous neuromyopathy which includes involvement of cerebrum, cerebellum, brainstem, peripheral nerve, neuromuscular junction and muscle[2,3]. Of these, subacute cerebellar degeneration as carcinomatous neuromyopathy is relatively rare[4].

On the other hand, myasthenia gravis-like easy fatigability may develop especially in cases with bronchial carcinoma, which is known as myasthenic syndrome or Eaton-Lambert syndrome[5]. The Eaton-Lambert syndrome is considered to be caused by deficient release of acetylcholine at the neuromuscular junction[6].

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It is the purpose of this paper to describe the clinicopathological findings of rare combination of subacute cerebellar degeneration and Eaton-Lambert syndrome occurred in a case with small cell anaplastic carcinoma of the lung.

CASE REPORT

Clinical History

A 55-year-old man was admitted to the Kawasaki Medical School Hospital on July 14, 1978 because of gait and speech disturbance.

He was well until early in June, 1978 when he began to feel easy fatigability in the lower extremities. On June 27 he lost his balance and staggered to the left on walking. Since then he began to have an unsteady gait. Early in July his speech became dysarthric. He felt that his palpebral fissure had become widened, and he had photophobia when looking at a distance.

He had smoked a package of cigarettes daily and drunk 90 ml of sake intermittently for over thirty years. At 19 years of age he had suffered from malaria in the Southeast Asia. He had pulmonary tuberculosis in his twenties, duodenal ulcer at forty-nine, and gastric ulcer at fifty-one. There was no family history of neurologic disease.

On admission, his temperature was 36.5°C, his pulse 58, and respiration 16. The blood pressure was 90/70 mm Hg. General physical examination revealed a poorly nourished man, whose mental status was intact. The pupils were equal and reactive. There was no nystagmus. His speech was slow and dysarthric. Rapid alternating movements of the upper extremities were awkward. The finger-to-nose test elicited slight unsteadiness. The knee-to-heel test and shin tapping test were ataxic. Muscle strength and deep tendon reflexes were normal in all extremities. There was no sensory impairment. The gait was wide-based and ataxic. When performing tandem gait he staggered after a few steps.

His urine was normal. The hematocrit was 42.8%. The white-cell count was 6,900, with a normal differential count. The erythrocyte sedimentation rate was 2 mm per hour. The serum protein was 5.9 g per 100 ml. Other chemical tests and electrolytes of the serum were all within normal limits. X-ray films of his chest revealed a nodular shadow in the right hilar region. The cytological examination of the sputum demonstrated malignant cells compatible with small cell anaplastic carcinoma of the lung. A lumbar puncture yielded clear, colorless cerebrospinal fluid that contained 40/3 mononuclear cells per cubic millimeter ; the protein was 29 mg, and the glucose 69 mg per 100 ml. An electroencephalogram and a computed axial tomographic (CT) scan of the brain was unremarkable. A motor nerve conduction velocity was 54.2 meter

in the right ulnar nerve, and 57.4 meter in the left tibial nerve per second. A sensory nerve conduction velocity was 63.7 meter in the right median nerve, and 37.2 meter in the left tibial nerve per second. An evoked electromyographic study showed a waning pattern with repetitive stimulations at low frequencies of 1, 3 and 5 Hz, whereas stimulations at high frequencies of 10, 20, 30 and 40 Hz produced a prominent waxing pattern after a short duration of waning pattern (Fig. 1).

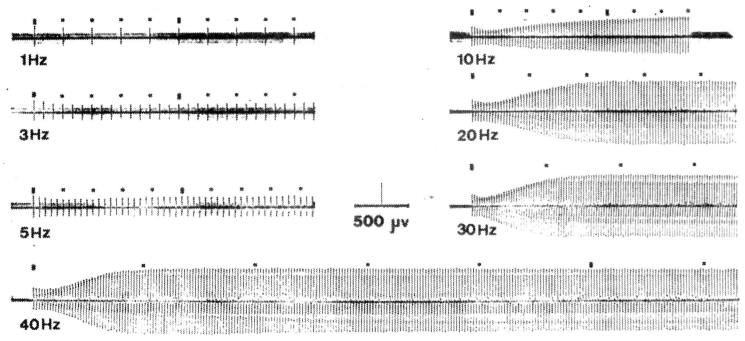

Fig. 1. The evoked electromyogram showing a waning pattern by low-frequency stimulations of 1, 3 and 5 Hz. While, high-frequency stimulations of 10, 20, 30 and 40 Hz elicit a prominent waxing pattern after a short duration of waning pattern.

After entry ataxia and dysarthria worsened further. Alternating movements of the tongue became slow. Again he felt the palpebral fissure had become widened, although ocular movements were full on physical examination. On July 24 he began to feel paresthesia in the sole of the feet. On July 31 radiotherapy was started. A few days later he felt a severe chest pain. His temperature rose to 38.4°C. A breathing sound had disappeared and dullness was noted in the right lower lung field. X-ray films of the chest revealed atelectasis and pleural effusion in the right lung field. Subsequently chemotherapy was supplemented. On August 15 nystagmus was noted on lateral gaze. Early in September he developed paresthesia in the tip of the tongue and fingers. In October radiotherapy was discontinued because of considerable improvement of the physical and roentgenological findings of the chest. He was discharged on November 2.

His conditions at home had remained stable until early in July, 1979 when he felt a pain in the lower part of the right scapula together with general fatigue, insomnia, anorexia and headache. One month later he became somnolent

and occasionally vomited. He returned to the hospital on August 7.

On second admission, the patient was markedly emaciated. On physical examination a hard mass of thumb's head size was palpated in the right supraclavicular fossa. Tenderness was elicited in the lower part of the right scapula. Breathing sound was inaudible and dullness was observed in the right chest below the level of the sixth rib. Neurologically ataxia and dysarthria appeared to have progressed still more. He could not walk any more for marked ataxia and, partly, for emaciation.

During his second admission dyspneic attacks repeated. From August 10 radiotherapy was resumed and oxygen inhalation was given. Early in September x-ray films of the chest revealed again atelectasis and pleural effusion in the right lung field. Anticancer drugs and antibiotics were administered. In November headache and vomiting had relapsed. A CT scan of the brain revealed low-density areas with ringed enhancement by contrast material in the left frontal, temporal and right occipital lobes (Fig. 2A). The lateral ventricles showed a band-like enhancement along its wall. Adrenocorticosteroid was prescribed. The level of his consciousness had been deteriorated. Choked biscs were observed in the ocular fundi. He died of respiratory insufficiency on December

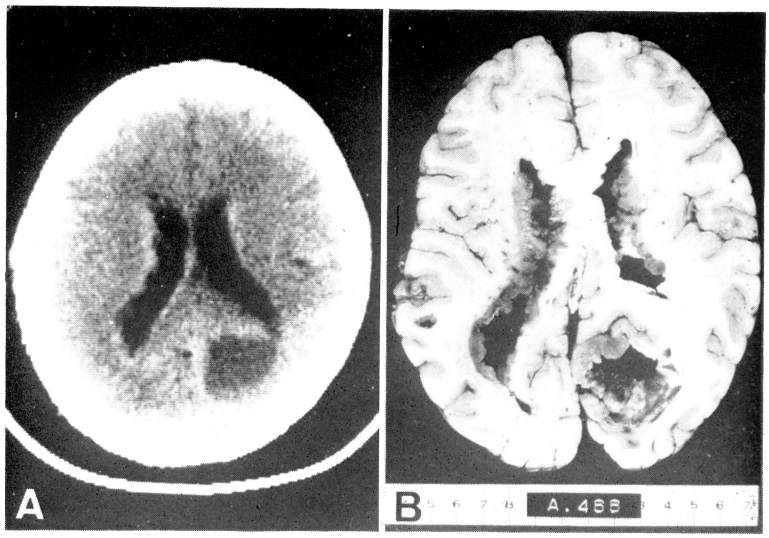

Fig. 2. A : CT scan of the brain revealing a low-density area with ringed enhancement in the right occipital lobe. The wall of the lateral ventricles is showing a band-like enhancement. B : The horizontal cut surface of the brain sectioned according to the CT scan phase showing a metastatic lesion in the right occipital lobe, the inside of which is cystic. The wall of the lateral ventricles is infiltrated all over by tumorous mass.

3, eighteen months after the onset of his illness.

Postmortem Examinations (A-466)

The examination of the lung disclosed a necrotic tumor mass of walnut size with a large cavity adjacent to the main bronchus of the right lower lobe (Fig. 3A). The wall of the bronchus was partially destructed by the infiltration of small round or oval cells with a hyperchromatic nucleus and scanty cytoplasm, forming nests or arranged trabecularly, which was consistent with small cell anaplastic carcinoma of the lung (Fig. 3B). Electron microscopy of the tumor cells did not reveal any neurosecretory granules.

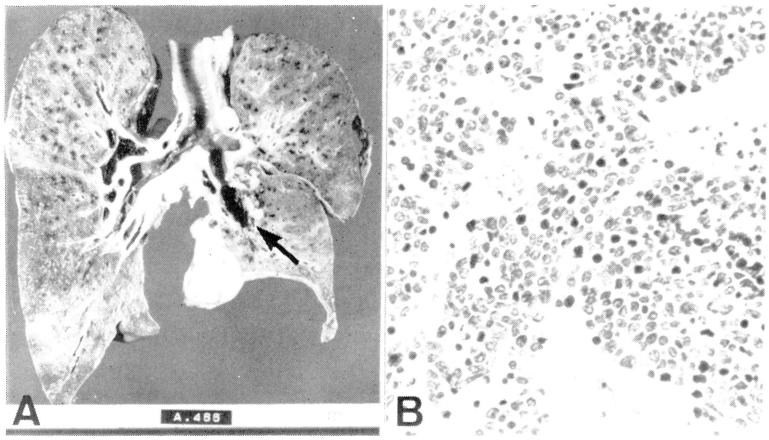

Fig. 3. A : Postero-anterior view of the lung. The arrow indicates a necrotic tumor mass with a large cavity adjacent to the main bronchus of the right lower lobe. B : The tumor cells are small round or oval with a hyperchromatic uncleus and scanty cytoplasm, forming nests or arranged trabecularly. HE, ×169.

The tumor had metastasized to the paratracheal, subcarinal, intrathoracic and para-aortic lymph nodes. Other pathologic findings of the lungs included bronchopneumonia with abscess formation, atelectasis, organizing pneumonia, obstructive pneumonitis, radiation pneumonitis with fibrosis, pulmonary edema, and an accumulation of pleural effusion of 630 ml in the right thoracic cavity. Additional examination of visceral organs demonstrated osmotic nephrosis, congestion and fatty metamorphosis of the liver, an erosion of the stomach, hypocellular bone marrow, and incidental chromophobe pituitary adenoma.

The brain weighed 1,420 g. The cerebral hemispheres were generally edematous and soft. Leptomeninges were congested. At the basal view, uncal herniatiations were seen bilaterally, more prominent on the left side. Arteries of the cerebral base were not so sclerotic. Examination of the horizontal cut

surface according to CT scan phases revealed two metastatic lesions of walnut size in the left temporal and right occipital lobes. The inside of them had become cystic due to necrosis (Fig. 2B). Lateral ventricles were slightly dilated. The wall of them was infiltrated extensively by tumorous mass. From the wall of the lateral ventricles the tumor was further infiltrated toward the deep white matter of the frontal lobe, forming a mass of cherry size. The third ventricle was filled with tumor mass. The wall of the fourth ventricle was also infiltrated by the tumor. The histology of tumor in the brain was identical with that of the lung.

The cerebellum was slightly atrophic and rather increased in consistency. On the histological examination of the cerebellum, the lesions were restricted almost exclusively to the paleocerebellum, namely, to the lingula, central lobule, culmen, declive, folium, tuber and pyramis of the vermis, and the anterior part of the quadrangular lobules of the hemispheres (Fig. 4A, 4B). The molecular layer of these portions had become considerably thin and loose. The Purkinje cells were almost completely lost and the Bergmann glia were diffusely proliferated in the Purkinje cell layer (Fig. 4C). The granular layer was also narrowed in thickness. The granule cells were slightly to moderately reduced in number. The cortex of the posterior part of the quadrangular lobule were only partially involved, with occasional atrophic Purkinje cells. Diffuse demyelination and proliferation of glial fibers were seen in the white matter under the involved cortex of the cerebellum. There was no inflammatory sign in these cerebellar lesions. The dentate nucleus had been relatively well preserved.

In the hippocampus, midbrain and pons were scattered small necrotic lesions with minor hemorrhages secondary to hippocampal herniations. The nerve cells of the pyramidal layer of the hippocampus had shown an ischemic nerve cell change. The nerve cells of the pontine nucleus outside of these vascular lesions in the pons, and of the inferior olivary nucleus were well preserved.

One micron section of the sural nerve embedded in epoxy resin had contained 7,650 fibers per square millimeter. Large myelinated nerve fibers appeared slightly reduced in number by the histogram. But abnormal findings such as active demyelination, axonal degeneration, cell infiltration or interstitial fibrosis were not apparent on the conventional light and electron microscopic study. The peroneus brevis muscle revealed no abnormalities light microscopically. Electron microscopic examination of the intercostal muscle, however, demonstrated occasional Z-line streaming and focal disarrangement of the myofilaments. The neuromuscular junctions were not detected.

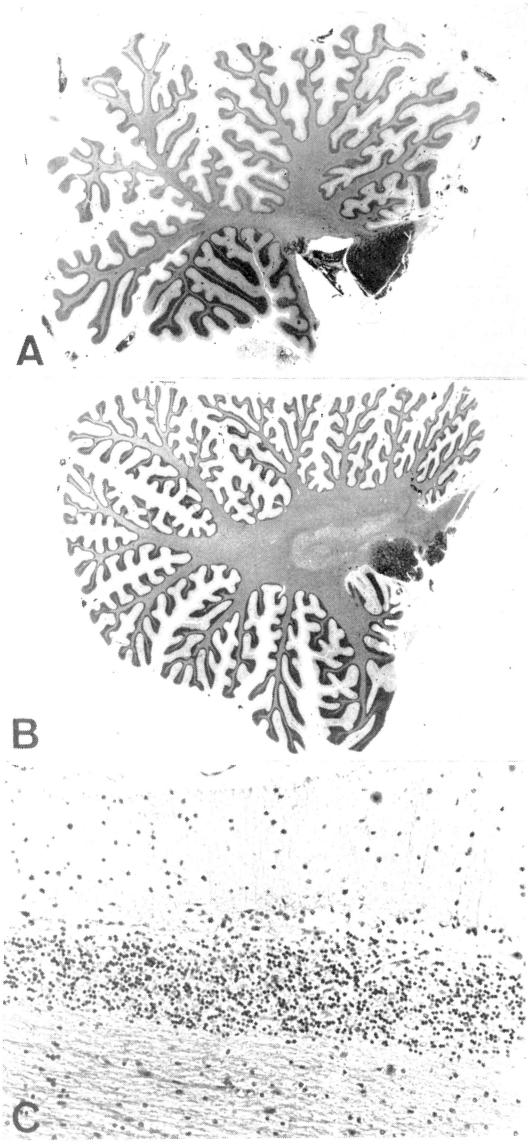

Fig. 4. The vermis A) and the right cerebellar hemisphere(B) of the cerebellum showing mild atrophy of the paleocerebellum. A. HE, ×1.9. B. HE, ×1.3. C : Photomicrograph of the cerebellar cortex of the paleocerebellum. The molecular layer is thin and loose. The Purkinje cells are totally lost and the Bergmann glia are moderately proliferated. Granule cells are also slightly reduced in number. HE, ×67.

DISCUSSION

The disorder of the patient described in this paper started with cerebellar symptoms and signs eighteen months before his death. The examination on the first admission revealed carcinoma of the lung. Since the evidence of the cerebral metastasis of the carcinoma was not given at that time, the pathological condition of the cerebellum was thought clinically to be subacute cerebellar degeneration as a remote effect of carcinoma of the lung[7]. The evoked electromyogram elicited waning pattern with low-frequency stimulations, while high-frequency stimulations produced prominent waxing pattern following a short waning pattern, consistent with the Eaton-Lambert syndrome[5].

Pathological examination of the lung eighteen months later revealed small cell anaplastic carcinoma. The brain showed cerebellar degeneration restricted only to the paleocerebellum, other than multiple metastatic lesions occurred in the last stage. Purkinje cells of the paleocerebellum were almost completely lost. The molecular and granular layers had also considerably degenerated. There were no inflammatory signs in the cerebellum. The peripheral nerves and muscles indicated only minimal changes. Regretfully pertinent neuromuscular junctions were not detected electron microscopically.

Carcinomatous neuromyopathy as a remote effect of malignant neoplasms has been recorded from the end of the last century[8]. It has drawn attention particularly since the symposium on "The Remote Effect of Cancer on the Nervous System" in Rochester, New York, U. S. A , in 1964, and the publication of the special edition of the Journal "Brain" in 1965 about this theme[9,10]. The accurate incidence of carcinomatous neuromyopathy is difficult to estimate because of occasional vagueness of diagnostic standard. Croft and Wilkinson[10,11] have reported as much as 16% in patients with carcinoma of the lung in man and 4.4% in those with carcinoma of the breast in woman. The subclassification of this disorder is not decisive, because the sites of lesions and their pathological features are quite variable. Generally it is subdivided into diffuse polioencephalitis with mental symptoms or brainstem lesions, subacute cerebellar degeneration, subacute necrotic myelitis, chronic myelopathy simulating motor neuron disease, sensory or sensori-motor neuropathy, polymyositis or dermatomyositis and myasthenic syndrome or Eaton-Lambert syndrome[3,4,8].

Of these, subacute cerebellar degeneration is one of distinctive clinicopathological syndromes encountered in some patients with malignant disease[1,9]. Historically, this unusual combination is said to originate from the report of Brouwer in 1919[12]. The relation of the two was investigated by Casper[13] in 1929, and Brain, Daniel and Greenfield[1] in 1951. As the pathogenesis of subacute cerebellar degeneration, various factors such as slow virus infection, immunological

derangement, allergic reaction, metabolic disorder, carcinotoxic or exogenous toxic effect, endocrine abnormality and hereditary predisposition are speculated similar to other carcinomatous neuromyopathies[8,14,15,16]. Of these, the most widespread view is the carcinotoxic one, which postulates that the neoplasm produces factors exerting a specific cytotoxic action on the cells of the cerebellar cortex, although there is no established theory at the present time.

Our patient was a 55-year-old man with bronchial carcinoma. Reviewing the literature, the age of onset of subacute cerebellar degeneration is most prevalent between fifties and sixties[9]. The two sexes are equally affected[9]. The incidence has not been computed. It seems apparently rare by comparison with carcinomatous neuropathies and myopathies[10]. As to the items of malignant neoplasms, bronchial carcinoma, especially of small cell anaplastic type, is exceedingly numerous in man[9], while in woman breast, uterus and ovarian carcinomas are common[9,17,18]. Occasional examples have been reported in association with tumors in other sites, including larynx[8], stomach[19], colon[20], urinary bladder[8] and prostate[21], and with malignant lymphoma[22,23,24] or leukemia[25].

Some cases develop cerebellar symptoms and signs in the course of malignancies. In others cerebellar symptoms and signs may initiate the disease as in the present case. The interval between the appearance of the neurological symptoms and the diagnosis of the malignant neoplasms spans one to ninety-six months[4,9]. Not rarely, the onset may be simultaneous. Neurological symptoms include acute or subacute progression of incoordination of the extremities, speech disturbance, ataxic gait and nystagmus. Occasionally, headache, dizziness or double vision precede these cerebellar symptoms, different from the usual spinocerebellar degeneration[9]. Cerebellar symptoms and signs may reduce in accordance with the treatment of malignancies[20,24,26], although ours did not show any remissions despite of the improvement of the carcinoma of the lung. On rare occasions, remissions may occur even while the tumor is actively progressing, as in a case of Messert and Blume[15]. Other than these cerebellar symptoms and signs, vertigo, dysphagia, ptosis of the eyelids, ophthalmoplegia, facial weakness, sensory impairment and mental changes are also described[9]. Our patient felt that his palpebral fissure had become widened and he had photophobia temporarily. Even if objective signs elucidating these symptoms were not obtained, these may show minor or subclinical involvement of the cranial nerves.

The macroscopic appearances in cases with subacute cerebellar degeneration show only minimal atrophy of the cerebellum. Microscopically the process affects primarily the cerebellar cortex[1,9]. Most cases show marked atrophy

and loss of Purkinje cells diffusely throughout the cerebellum. The molecular and granular layers are also variably degenerated. The cerebellar white matter shows changes secondary to the loss of Purkinje cell axons. There may be some rarefaction of myelinated fibers with corresponding reactive gliosis. Incidentally the dentate nucleus, inferior olivary nucleus, subthalamic nucleus, pontine nucleus, posterior column of the spinal cord, spinocerebellar tract and pyramidal tract may also be involved[1,9,14]. Compared with these findings, our case showed degeneration restricted only to the paleocerebellum. From the view point of these cerebellar features of our patient, ours are rather resembling to the cerebellar degeneration due to alcoholic intoxication, deficiency, or Holmes' familial cerebello-olivary atrophy[27]. However, our patient was never an alcoholic and under nutritionally deficient state at the time of the onset of the cerebellar symptoms and signs. The presence of carcinoma might possibly put him into the similar situation as in alcoholic or in deficient state. Inferior olivary nucleus was not involved in our case, unlikely of Holmes' familial cerebello-olivary atrophy. Zülch[28], and Dazzi and Ferrari[19] have also described a more severe loss of nerve cells in the vermis than in the hemispheres as in our case. Anyway, localized degeneration within the vermis and the superior surface of the cerebellar hemispheres may occur in the cases with subacute cerebellar degeneration.

In spite of inflammatory reaction was not observed in our case as well as many other cases, some cases[1,17] are indicating prominent inflammatory reaction. And yet, it is interesting that clinically even in our case the cerebrospinal fluid in the early stage showed a mild pleocytosis, which may suggest a reaction to rapidly degenerating cerebellum, different from chronic progressive degenerative disease.

Another outstanding characteristic of the present case is that the evoked electromyographic studies have demonstrated a distinctive pattern compatible with Eaton-Lambert syndrome, though typical electron microscopical findings of the neuromuscular junctions seen in Eaton-Lambert syndrome were not detected.

The Eaton-Lambert syndrome is said to be seen in 0.1% of the whole bronchial carcinoma and further in 6% of small cell anaplastic carcinoma of the lung[12]. Coexistence of subacute cerebellar degeneration and Eaton-Lambert syndrome as in our case is still rarer. Only three autopsy verified cases with this combination are described in literature[6,29,30]. Furthermore, mild neuropathy was suggested in our case, as a clinical case of multiple neurologic paraneoplastic syndromes described by Zweifel and Albers[31]. For its common etiological mechanism, possible humoral or toxic agent released by the neoplasm may be taken into consideration, other than peptides released from the neurosecretory

granules, which were not found in our case. At any rate, subclinical Eaton-Lambert syndrome may be more frequently detected when evoked electromyogram is carried out routinely on the patients with a malignant neoplasm.

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