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Abstract

A 67-year-old male patient initially showed memory disturbance followed by tremors a year later. The symptoms rapidly aggravated to dementia and Parkinsonian symptoms, and the patient died 2 years and 6 months after the onset at the age of 69 years and 5 months. Autopsy revealed numerous senile plaques in the cerebral cortex and Alzheimer's neurofibrillary tangles in the inferior temporal lobe and hippocampus. A number of Lewy bodies were found in the cerebral cortex and brain stem. Lewy bodies were found abundantly in the third layer of the pyramidal cells in the gyrus parahippocamalis. The distribution of Lewy bodies in the cerebral cortex was similar to that of inflated cells in Pick's disease.

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Diffuse Lewy Body Disease: An Autopsy Case

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A 67-year-old male patient initially showed memory disturbance followed by tremors a year later. The symptoms rapidly aggravated to dementia and Parkinsonian symptoms, and the patient died 2 years and 6 months after the onset at the age of 69 years and 5 months. Autopsy revealed numerous senile plaques in the cerebral cortex and Alzheimer's neurofibrillary tangles in the inferior temporal lobe and hippocampus. A number of Lewy bodies were found in the cerebral cortex and brain stem. Lewy bodies were found abundantly in the third layer of the pyramidal cells in the gyrus parahippocamalis. The distribution of Lewy bodies in the cerebral cortex was similar to that of inflated cells in Pick's disease.

Key words : dementia, Parkinsonism, diffuse Lewy body disease, Pick's inflated cells

A Lewy body is an eosinophilic inclusion body that is observed in monoamine neurons in the brain stem, especially in the substantia nigra and locus ceruleus of patients with Parkinson's disease. Cases in which Lewy bodies are found not only in the brain stem, but also in the cerebral cortex, have aroused interest since reported by Kosaka *et al.* (1) in 1976. But only a few cases have been reported (2-15).

Case Report

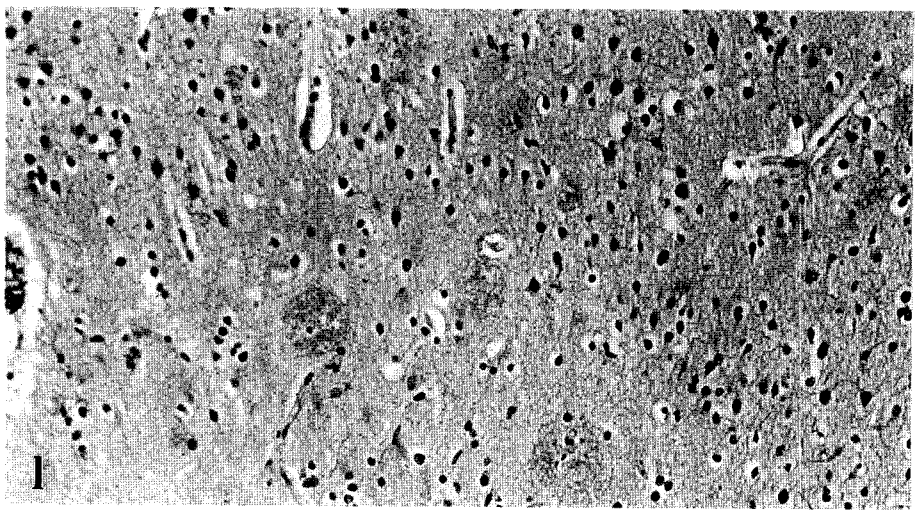
The patient was a 69-year-old male. His family history was noncontributory. He had a past history of an operation for duodenal ulcer at the age of 49 years and a hemorrhoidectomy at the age of 60 years. He first recognized having memory difficulty at the age of 67 years. The memory disturbance and amnesia became so severe that he was unable to work. He had visual hallucinations day and night, and would say such things as : "there is a snake" and "a thief has entered our house". At the same time, tremors occurred in his right arm, and the patient was diagnosed as having Parkinson's disease. Drugs were given, but the patient stopped taking them because he felt that his motion was restrained during the drug therapy. He was hospitalized in a psychiatric hospital one month later because of irritation and insomnia. His mental symptoms became worse. Due to night delirium, urinary incontinence, general consumption and decubitus, the patient was transferred to Okayama National Hospital. He was lethargic, had a vacant look, and was unable to respond correctly. It was difficult to communicate with him. He slept unless he was stimulated. No neurological changes were observed in the cranial nerves. Articulation was not clear as the patient scarcely opened his mouth. Rigidity was found in the neck. Muscle tone was increased in the upper extremities (left > right). Muscular rigidity and the cogwheel phenomenon were also observed in the arms. His knees were bent, and muscular rigidity and "Gegenhalten" was observed in the lower extremities. Deep tendon reflexes were normal. The sensory system, standing posture and gait could not be examined. Although the

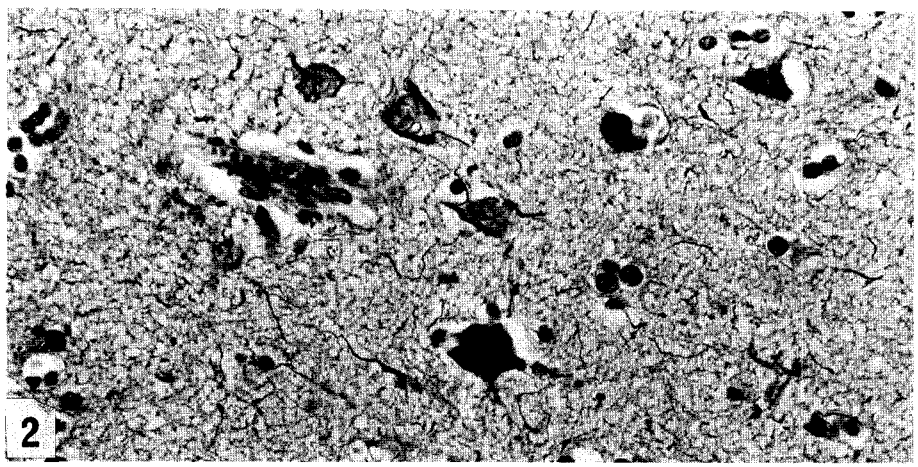
patient slept throughout day, he responded "yes", when called to and spoke a few words that were followed by inaudible murmurs before he fell asleep again. He knew his name and could identify his wife, but mistook the date and could not remember the name of most of his children. He stated his occupation and speciality correctly and made professional conversation which was, however, inappropriate to the situation. For example, he said to the nurses,"I'll examine you and draw an anatomical illustration of your ear and nose". Anemia (RBC 3,050,000/mm^3, Hb 9.9 g/dl, Ht 29.5%), leucocytosis (11,200/mm^3, Seg. 88. Ly 11), CRP +4, RA (−), and a decrease in serum protein (5.7 g/dl) were found in the examination of a peripheral blood sample. Other laboratory data including electrolytes and hepatic and renal function were normal. In EEG, the basic activity was low amplitude fast waves with no alpha waves. Periodic synchronous discharges (PSD) were not seen. Examination of cerebrospinal fluid revealed an initial pressure of 175 mmH_2O, 35 mg/dl protein, 96 mg/dl glucose and a cell count of 5/3. Cranial Xray-CT revealed slight atrophy of the cerebral cortex and enlargement of the lateral ventricles. In the earlier days of his admission, the patient slept most of the time, but later he stayed awake more during the day time. Disorientation, misidentification of persons and urinary incontinence continued. He slept well at night and no delirium was observed. He was transferred to another department in the hospital for the treatment of decubitus and returned home later. However, communication with his wife became difficult, and food intake gradually decreased. He finally became bed-ridden and required full care and nursing. He was unable to take food and fell into shock. Various resuscitation attempts failed, and he died at the age of 69 years and 5 months. The course of this case was 2 years and 6 months.

Autopsy Findings

The brain weighed 1,100 g. Numerous clusters of minute subdural hematomas up to 3 mm in diameter were found bilaterally. Atrophy of the brain was not clear. Leptomeninges were opaque in the frontal and parietal lobes. A moderate degree of atherosclerosis was found in the basilar artery. The cut surface of the brain showed a well balanced proportion of gray matter to white matter. Focal softenings and lacunae were not present. Microscopy revealed a diffuse distribution of senile plaques composed equally of primitive plaques and typical plaques (Fig. 1). "Drusige Entartung", in which senile plaques look as though they permeate from the vascular wall, was frequently observed. Many Alzheimer's neurofibrillary tangles were found in the Ammon's horn, gyrus parahippocampalis, gyrus tempolaris medius and gyrus tempolaris inferior (Fig. 2), but few were observed in other areas.

Many Lewy bodies were observed in the neurons especially in the insula, cingulate gyri and frontal and temporal lobes of the cerebrum. Fewer were observed in the parietal lobe, and very few were identified in the occipital lobe. Lewy bodies were mainly found in small cells in deep layers (Fig. 3). The staining properties of these Lewy bodies were : faintly pink by Hematoxylin and Eosin (H-E), faintly blue by Azan stain, negative by Periodic Acid Schiff reaction, white by Nissl stain, negative by Congo-red stain, and slightly argyrophilic by Bodian stain. In the cingulate, Lewy bodies were found not only in neurons of the fifth and sixth layers, but also in the third layer of the pyramidal cells (Figs. 4a & b). In the gyrus parahippocampalis, many Lewy bodies were present. They were strongly stained red with eosin and surrounded by white halos, resembling those in the brain stem (Figs. 5a & b). In this gyrus, few Lewy bodies were found in the deep layers. In both the caudate and putamen, two intra-neuritic type of Lewy bodies were observed. Only one intraneuritic Lewy body was found in the thalamus. Thalamic inclusion bodies were demonstrated in the medial nucleus. The number





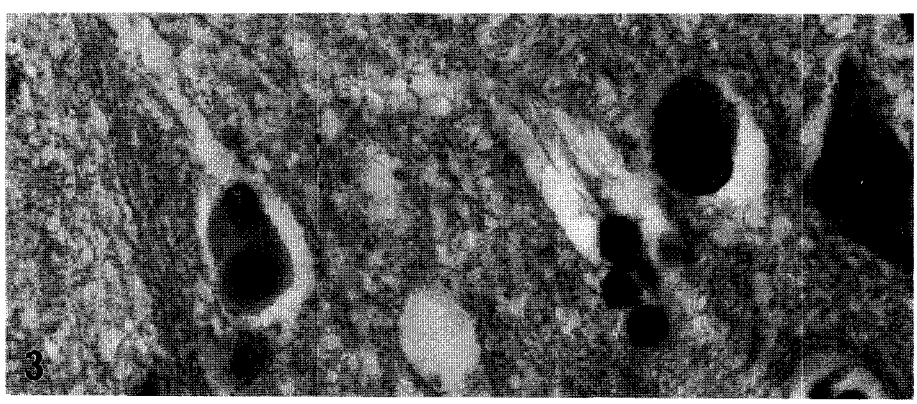
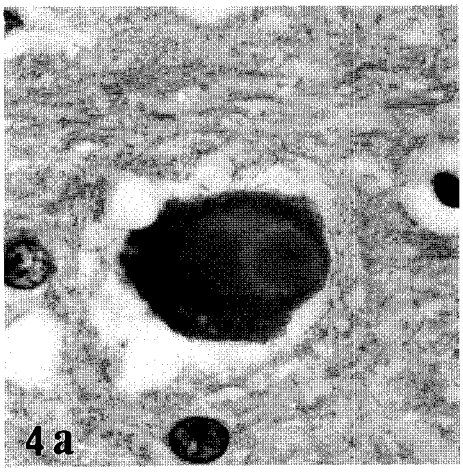
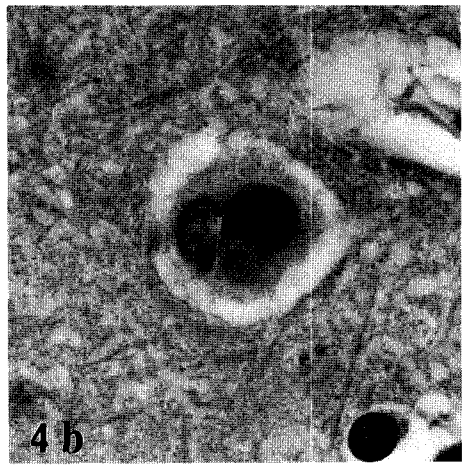
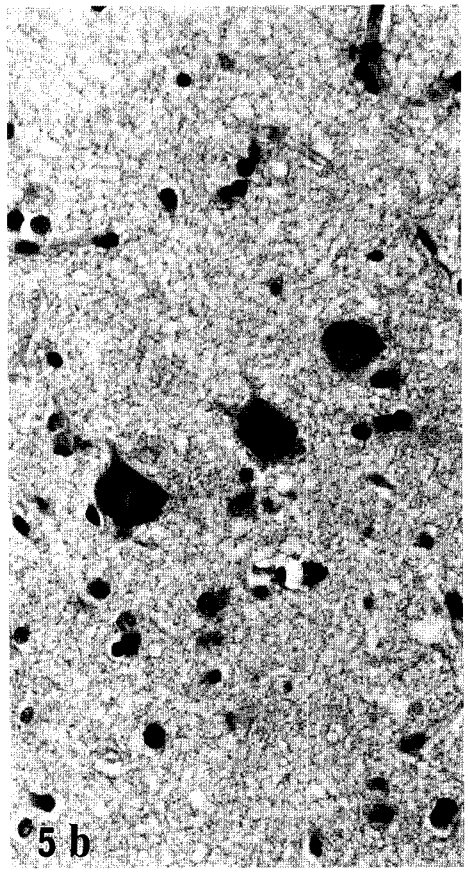


Fig. 1 Senile plaques in the frontal cortex. Bodian, ×170.
Fig. 2 Neurofibrillary tangles in the inferior temporal cortex. Bodian, ×340.
Fig. 3 Cerebral type of Lewy bodies in the frontal cortex. Hematoxylin-eosin, ×850.





Figs. 4a & b Lewy bodies in the pyramidal cells of the cingulate. Hematoxylin-eosin, ×850.



Figs. 5a & b Lewy bodies in neurons of the third layer in the parahippocampal gyrus. Hematoxylin-eosin, a; ×85, b; ×340.

of neurons markedly decreased in the nucleus basalis of Meynert in the substantia innominata where Lewy bodies were observed in the neurons and neurites of the remaining cells. Alzheimer's neurofibrillary tangles were observed, although the incidence was not high. Lewy bodies were found in many cells of the amygdalae. There were round inclusion bodies that resembled Lewy bodies, but that stained faintly blue by H-E and were moderately argyrophilic. Their morphological and staining properties suggested that these inclusion bodies were neurofibrillary tangles (globose type). The number of melanin-containing cells in the substantia nigra decreased in its central parts, while typical Lewy bodies were abundant in the remaining neurons. Furthermore, melanin migrated into the parenchyma, and some phagocytes contained melanin (Fig. 6). Astrocytic gliosis was also observed. Few neurons and intracytoplasmic Lewy bodies were observed in the locus ceruleus in the pons. Some Lewy bodies were found in the griseum centrale pontis and reticular formation. The nuclei pontis looked normal, and no Lewy bodies were found. Transverse fibers of the pons were normal. Lewy bodies were observed in the nucleus dorsalis nervi vagi in the medulla oblongata. No significant changes were found in the nucleus dentatus or cerebellar cortices.

Discussion

This patient first experienced deterioration of memory at the age of 67 years. Tremors appeared one year later. Then, sleep disturbance occurred, starting with insomnia which was followed by somnolence. Rapid aggravation of Parkinsonian symptoms was followed by the patient's death 2 years and 6 months after the first symptoms. Lewy bodies were observed throughout the cerebral cortices and brain stem. A number of senile plaques were observed in the cerebral cortices. These clinical and pathological findings coincide with the Lewy body dis-

Fig. 6 Neuronal loss, astrocytic gliosis and an intracytoplasmic Lewy body in the substantia nigra. Hematoxylin-eosin, ×170.

ease group A proposed by Kosaka *et al.* (7) or diffuse Lewy body disease reported by Yoshimura (10). The rapid aggravation of memory disturbance to dementia with amnesia, disorientation and misidentification of persons within a 6-month period was suggestive of Creutzfeldt-Jakob disease, which however, was discounted on the basis of the absence of myoclonus and periodic synchronous discharges (PSD) in the EEG. The present case was diagnosed as senile dementia of the Alzheimer type with Parkinsonian symptoms. Although the patient became somnolemt immediately after hospitalization, the arousal time did increase gradually. Communication was hardly possible even when the patient was awake, indicating that the underlying dementia was accompanied by disturbance of consciousness. His utterances such as "I'll examine you" and "I'll put a cotton ball in your nostril" suggest the occurrence of occupational delirium. Symptoms of Lewy body disease, especially of group A, are similar to those of Alzheimer's disease and of senile dementia of the Alzheimer type. These diseases start with the deterioration of memory retention and amnesia, and the symptoms proceed with the concomitant occurrence of depression and hallucination in some cases. These symptoms may occur frequently, since senile plaques and neurofibrillary tangles concomitantly occur in the cerebral cortex of patients with group A Lewy body disease. Maruyama *et al.* (13) reported a case of Lewy body disease in which changes in the awake-sleep rhythm were observed. In this case, peduncular hallucination, mental symptoms, insomnia and somnolence continued over 2 years, and an overnight polygraph demonstrated stage 1 REM (rapid eye movement). Histopathological examination indicated degeneration of the monoamine neurons in the substantia nigra, locus ceruleus and nucleus raphe. The present patient had disturbance of consciousness including somnolence at the time of admission. This episode was assumed to be related to the appearance of Lewy bodies in the locus ceruleus, nucleus raphe and reticular formation. The Lewy bodies in the cerebral cortex were distributed chiefly in the temporal and frontal lobes, insular cortex and cingulate gyrus. These Lewy bodies were mainly found in small neurons in the deep layers of the cortex. They were also frequently found in the nucleus amygdalae. Such distribution reminds one of Pick's disease which is characterized by lobar atrophy in the frontal and temporal lobes as well as by aryrophilic cells and inflated cells. Inflated cells in Pick's disease chiefly appear in the temporal and frontal lobes, gyrus insula and gyrus cinguli, particularly in the deep layers such as the fifth and sixth layers. The Lewy bodies in the present case showed a similar distribution, but differences between the cortical Lewy bodies and Pick's inflated cells were noted by microscopic and electron-microscopic observations. In view of the pathological significance of Lewy bodies in the cerebral cortex, a distribution similar to Pick's inflated cells suggests that dementia in Lewy body disease may present similar mental symptoms as Pick's disease. Actually, cases previously reported by Kosaka *et al.* (5), Kuroda *et al.* (4), and Momma *et al.* (8) had some clinical features similar to those of Pick's disease, while the majority of cases of Lewy body disease manifested dementia of the Alzheimer type, and not of Pick's disease, as in the present case. The present case was characterized by the appearance of Lewy bodies in the gyrus parahippocampalis, especially in the third layer. As for the distribution of dopaminergic neurons in the brain, an investigation of the rat's brain by Lindvall *et al.* (16) revealed that the terminals of projections from A10 were in the prefrontal area, entorrhinal cortex and anterior part of gyrus cinguli. Al-

thogh few in number, Lewy bodies were recognized in the third layer of the anterior cingulate gyrus of the present case. A case showing the same distribution of Lewy bodies was reported by Eggertson & Sima (17). We investigated the gyri parahippocampalis of two other patients and found Lewy bodies in the superficial layer (the third layer), althogh there were few per slide.

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