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Case Report

Sudden unexpected death in early Parkinson's disease: neurogenic or cardiac death?

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ABSTRACT

We present two cases of sudden unexpected death (SUD) in elderly individuals in whom autopsy unexpectedly showed Lewy pathology, a hallmark of Parkinson's disease. Both individuals were 68-year-old men who were found dead in their homes without lethal trauma or poisoning. Inquests into their deaths suggested that nonmotor cardiovascular signs of Parkinson's disease might have appeared just before their deaths, although few typical motor signs were present. Autopsy showed Lewy pathology in the heart and peripheral autonomic nervous system in addition to lesser involvement of the brainstem that was consistent with Braak stage 3. In case 1, an atrial septal defect of the secundum type with advanced fibrosis of the atrium was present. In case 2, severe stenosis of the atrioventricular node artery with some microscars and diffuse interstitial fibrosis of the basilar ventricular septum were found. These two cases show some premotor Parkinson's disease with a symptom suggestive of autonomic dysregulation which may be a risk of SUD. In addition, coexistence of structural change of the heart with possibly arrhytthmogenic potential may increase the risk of SUD with Parkinson's disease. Present two cases showed neuropathological examination to detect Lewy pathology in the peripheral nervous system may be important for revealing the cause of some cases of SUD in the elderly, even if typical motor signs were not evident before death.

1. Introduction

The histological hallmark of idiopathic Parkinson's disease (PD) is Lewy pathology (LP), including Lewy bodies in cell somata and thread-like Lewy neurites, both composed primarily of phosphorylated α-synuclein [1]. Recent clinicopathological studies have revealed that individuals with PD show various nonmotor signs [1–3]. These nonmotor signs are also related to the deposition of phosphorylated α-synuclein and tend to appear earlier than the typical motor signs. An individual with LP who has not yet developed typical motor signs is considered to have premotor PD [2,3].

Although the prevalence of premotor PD has not yet been determined, autonomic dysfunction related to PD has been considered a major contributor to sudden unexplained death (SUD) in patients with PD [4,5]. However, we have found very few pathological reports that have included detailed cardiac pathology of SUD in patients with PD. Here, we present the cases of two elderly men with SUD whose autopsies showed unpredicted LP.

2. Case descriptions

Case 1 involved a 68-year-old man who was found dead at his home. He had retired from farming 5 years previously. Although a police examination showed that he had had no documented clinical history for at least the previous 10 years, his relatives noticed that he had developed a staggering gait 1 month before his death. He had not visited a hospital despite the recommendations of his relatives.

The autopsy showed some fresh and old bruises of the extremities. Almost all of the bruises were found on body parts such as knees and elbows, consistent with falling as the most probable cause of these injuries. There were no fractures or injuries to blood vessels or organs. The brain weight was 1380 g. No focal lesion or substantial atrophy of any region was evident. Only mild depigmentation of the substantia nigra was observed (Fig. 1A). The heart weighed 350 g, and an atrial septal defect (ASD) of the secundum type, with a diameter of about 1 cm, was found. Mild right ventricular hypertrophy was present, but no dilatation of the right ventricle or displacement of the ventricular septum toward the left ventricle, which are signs of pulmonary

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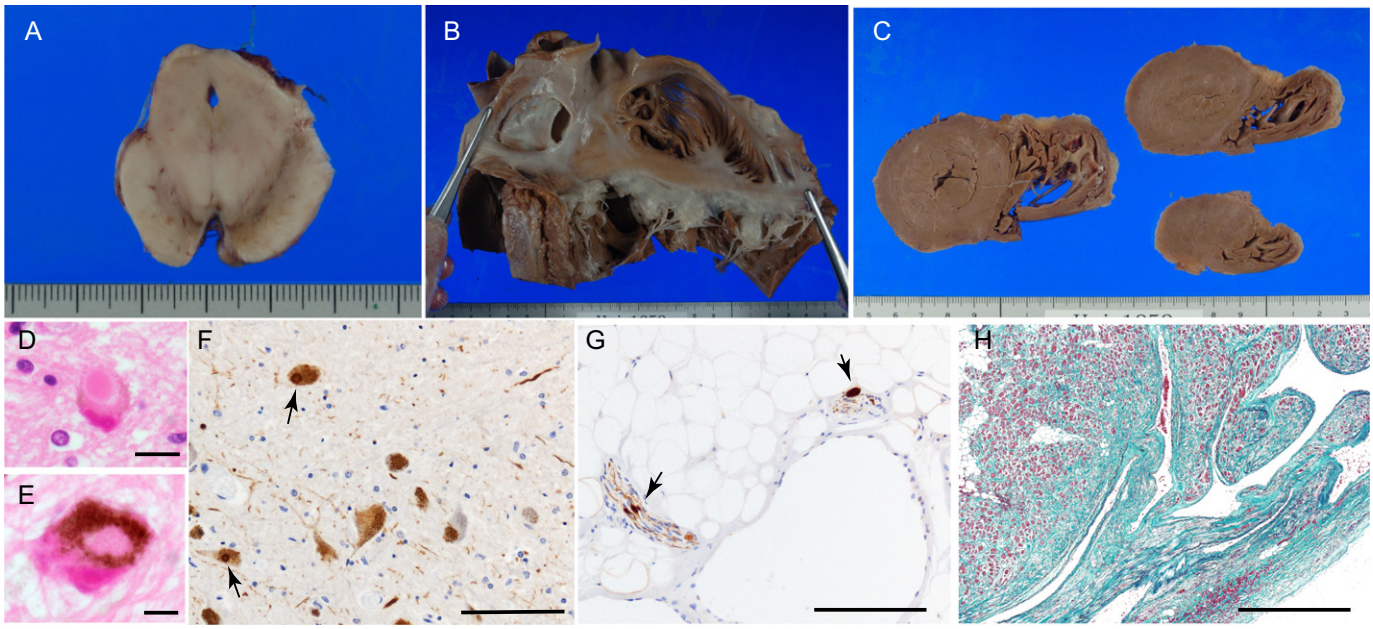

Fig. 1. Pathological appearance of case 1. (A) Horizontal section of midbrain showing depigmentation of the substantia nigra. (B) Gross appearance of the right side of the heart includes an atrial septal defect. (C) Horizontal section of the ventricles shows mild thickening of the right ventricular wall. (D, E) A cell containing a Lewy body (D) and a pale body (E) in the substantia nigra. (F) α-Synuclein-positive Lewy pathology in the substantia nigra. Arrows show intracytoplasmic inclusions. (G) Phosphorylated-α-synuclein-positive Lewy pathology in peripheral nerve fibers of the pericardium. (H) Severe interstitial fibrosis of the right atrium of the heart (Elastica–Masson). Scale bars=10 μm (D, E), 100 μm (F), 200 μm (G), 500 μm (H).

hypertension, were evident (Fig. 1B, C). A full toxicological examination was negative.

Microscopic examination showed some Lewy and pale bodies in the substantia nigra, pontine tegmentum, and medulla oblongata, including the dorsal motor nucleus of the vagus and nucleus ambiguus (Fig. 1D, E). No neuronal loss beyond that expected from normal aging was evident in any region. Immunohistochemistry using an antibody against phosphorylated α-synuclein (clone LB508, 1:500; Zymed, San Francisco, CA, USA) showed LP in the brainstem, olfactory bulb, and peripheral nerves in both the pericardial and myocardial layers of the both atria and ventricles of the heart (Fig. 1F, G), consistent with Braak stage 3. No structure was positive for β-amyloid (clone 6F/3D,

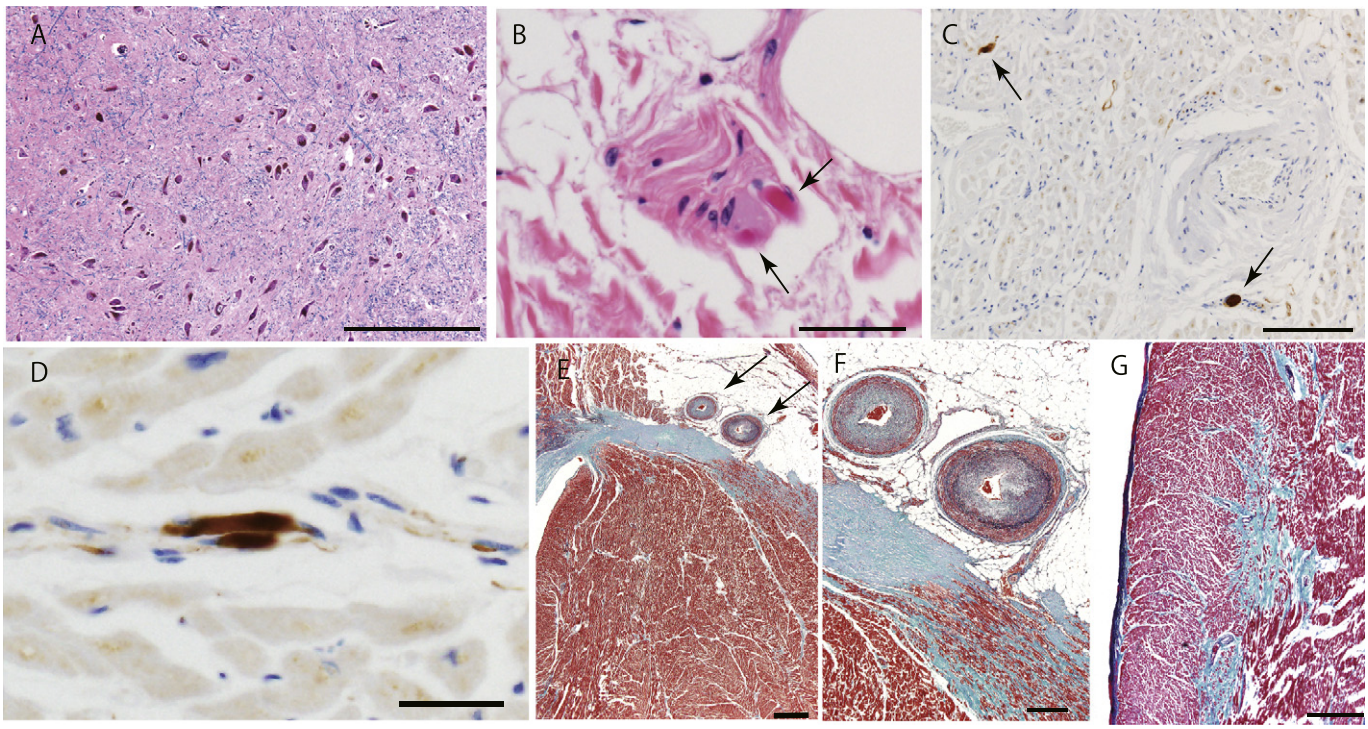

Fig. 2. Histopathology of case 2. (A) Mild neuronal loss in the substantia nigra (Luxol fast blue/hematoxylin eosin). (B) Lewy bodies in a peripheral nerve of the pericardium, (hematoxylin–eosin). (C, D) Accumulation of phosphorylated α-synuclein in a peripheral nerve in the cardiac myocardium. (E) Histological appearance of the basilar ventricular septum. Arrows indicate the atrioventricular node artery (Elastica–Masson). (F) High-power view of atrioventricular node artery with severe stenosis. (G) Microscarring and interstitial fibrosis in the basilar ventricular septum (Elastica–Masson). Scale bars=200 μm (A), 20 μm (B, D), 100 μm (C), 1 mm (E), 500 μm (F), 50 μm (G).