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【 CASE REPORT 】

Multimodal Imaging of Constrictive Pericarditis Induced by Long-term Pergolide Treatment for Parkinson's Disease

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Abstract:
We herein report the first case of constrictive pericarditis (CP) induced by long-term pergolide treatment for Parkinson's disease that was assessed using multimodal imaging in a 72-year-old patient with leg edema and dyspnea. The patient was correctly diagnosed with CP using multimodal imaging and successfully treated with pericardiectomy. The treatment history of Parkinson's disease and pathological findings of the removed pericardium suggested that long-term pergolide was the cause of CP. Properly recognizing pergolide as the cause of CP and accurately diagnosing CP using multimodal imaging may contribute to the early detection and treatment of pergolide-induced CP.

Key words: Constrictive pericarditis, Multimodal imaging, Parkinson's disease, Pergolide

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Introduction

Case Report

A 72-year-old man with a history of Parkinson's disease was admitted to our department with diuretic-resistant (azosemide 40 mg/day) leg edema and dyspnea lasting for 2 months. Parkinson's disease had been diagnosed 40 years previously, and he had been treated with anti-parkinsonian agents, such as pergolide mesylate (500 μg/day), levodopa (300 mg/day), benserazide hydrochloride (75 mg/day), and selegiline hydrochloride (7.5 mg/day), for approximately 20 years. He had no history of chest radiation or open-heart surgery.

A physical examination on admission revealed that he was 164 cm tall and weighed 77 kg. His body mass index was 28.6 kg/m^2. He was apyrexial. His pulse rate was 85/min, blood pressure was 111/68 mmHg, and transcutaneous oxygen saturation was 96% in room air. Paradoxical pulse, jugular venous distention, Kussmaul's sign, and leg edema were observed, while pericardial rub was not.

Laboratory tests revealed increased levels of serum N-terminal pro-B-type natriuretic peptide (3,426 pg/mL), creatinine (2.04 mg/dL), aspartate aminotransferase (36 U/L), and alkaline phosphatase (371 U/L). The results of screening blood tests for viral, bacterial, or fungal infections, including tuberculosis; connective tissue diseases; and malignant tumors were negative.

Chest radiography revealed mild cardiomegaly (cardiothoracic ratio, 53%) and bilateral pleural effusion with no pericardial calcification. Electrocardiography revealed sinus rhythm and low voltage with no significant ST-segment changes. Echocardiography demonstrated a normal left ventricular (LV) end-diastolic dimension (46 mm), LV ejection fraction (70%), and no LV hypertrophy. No significant valvular disease was present, although thickening of all valve leaflets was observed. Pericardial thickening, septal bounce

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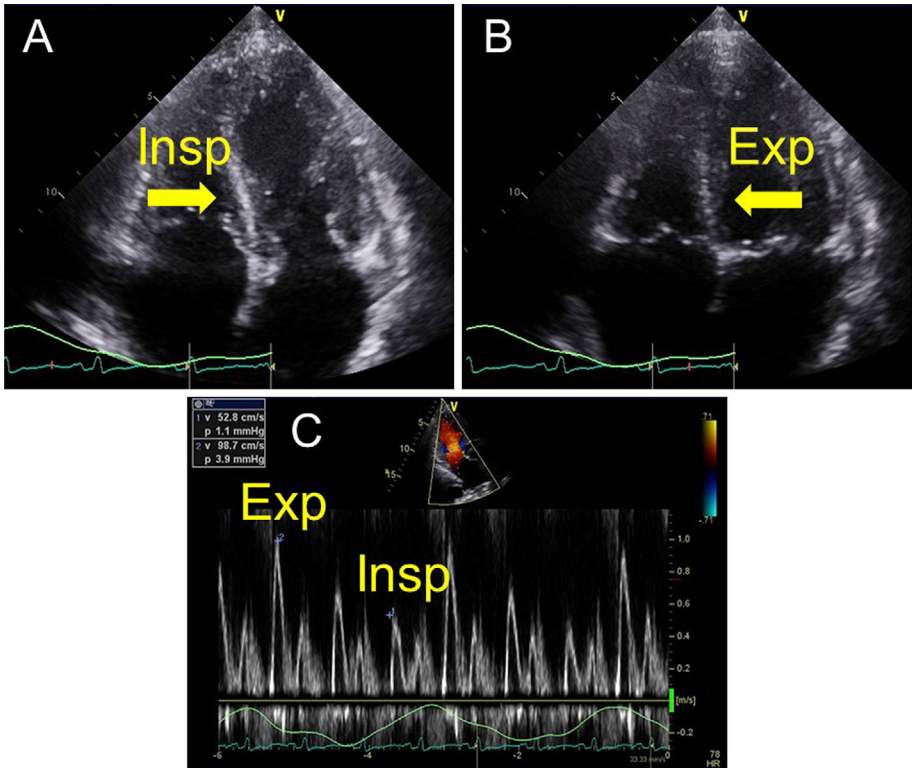

Figure 1. **(A, B) Apical four-chamber echocardiographic view demonstrating the leftward ventricular septal shift during inspiration (yellow arrows). (C) Pulsed-wave Doppler recording at the level of the open mitral leaflet tips in the apical view showing an inspiratory decrease and expiratory increase in early mitral inflow velocity. Exp: expiration, Insp: inspiration**

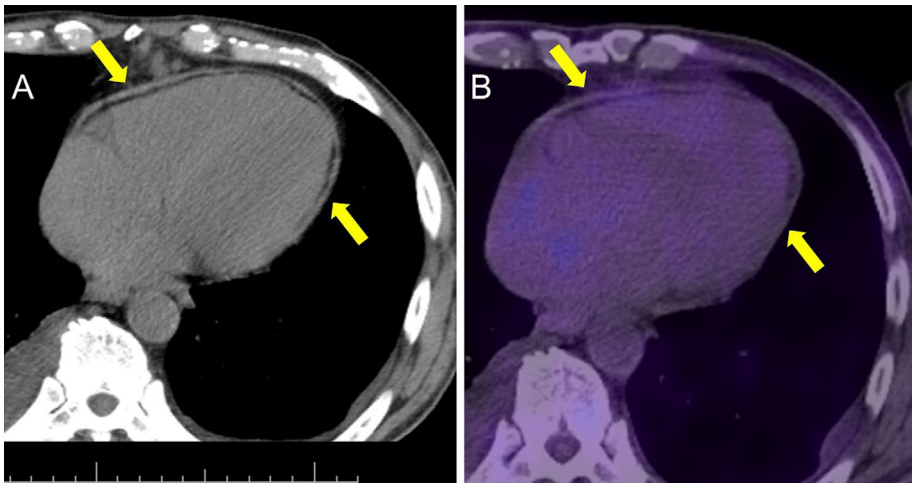

Figure 2. **(A) CT scan of the heart demonstrating the significantly thickened pericardium (5 mm) (yellow arrows) with no pericardial calcification. (B) FDG positron emission tomography revealing no abnormal FDG uptake in the pericardium (yellow arrows).**

with the inspiratory motion of interventricular septum (Fig. 1A, B, Supplementary Video 1), respiration-related changes in mitral E velocity (47%) (Fig. 1C), higher mitral than lateral annular e' velocities (septal e' 13.5 cm/s vs. lateral e' 10.5 cm/s), and dilation of the inferior vena cava (26 mm) were observed. These echocardiographic findings were considered suggestive of constrictive pericarditis (CP).

Computed tomography (CT) of the heart revealed a significantly thickened pericardium (5 mm) with no pericardial calcification (Fig. 2A). 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) showed no abnormal FDG uptake in the pericardium (Fig. 2B). Cardiac magnetic resonance (CMR) imaging also indicated a thickened pericardium (Fig. 3A, Supplementary Video 2), and two-dimensional CMR tissue tracking demonstrated reduced peak strain values at the LV basal anterolateral and inferior walls, indicating pericardial adhesions (Fig. 3B).

The patient underwent cardiac catheterization. Coronary

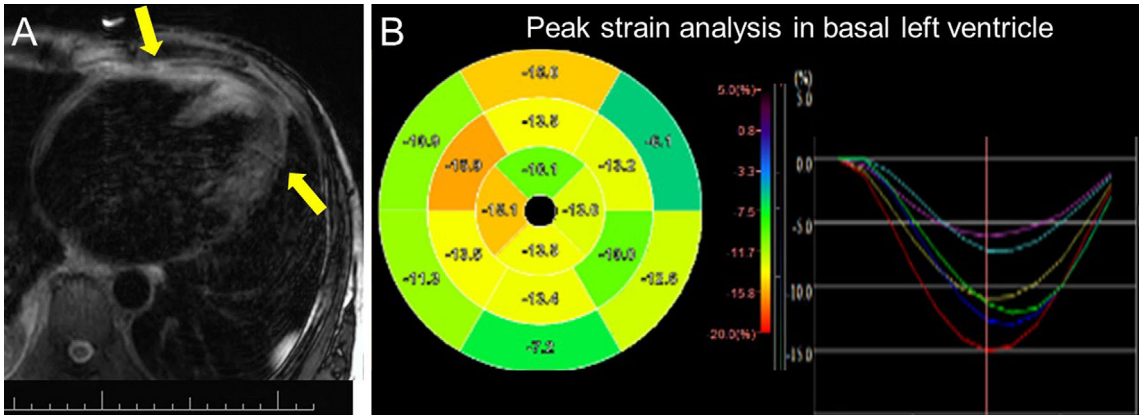

Figure 3. **(A) CMR imaging demonstrating the thickened pericardium (yellow arrows). (B) Two-dimensional CMR tissue tracking revealed the reduction in the peak strain values at the LV basal anterolateral (purple line) and inferior (light blue line) walls.**

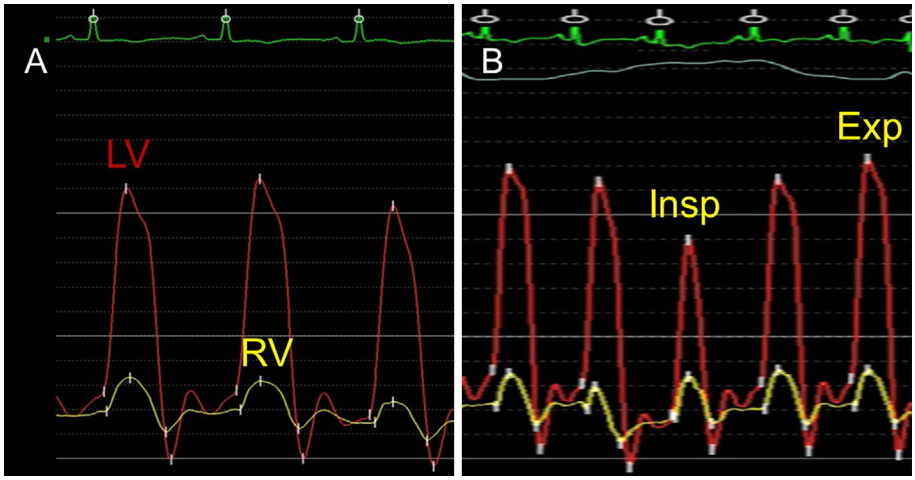

Figure 4. **(A) Simultaneous pressure tracing of the left (red line) and right (yellow line) ventricles demonstrating elevated and similar end-diastolic pressures and dip-and-plateau patterns. (B) Discordant changes in the left (red line) and right (yellow line) ventricular systolic pressure during respiration. LV: left ventricle, RV: right ventricle, Exp: expiration, Insp: inspiration**

angiography revealed no stenotic lesions. Right atrium (RA) pressure tracing revealed an elevated mean RA pressure (23 mmHg) with a prominent Y descent. The pulmonary artery pressure was 38/25 mmHg, and the mean pulmonary capillary wedge pressure (28 mmHg) was elevated, reflecting strong congestion. Simultaneous pressure tracing of the left and right ventricles revealed elevated, similar end-diastolic pressures and dip-and-plateau patterns (Fig. 4A), as well as ventricular interdependence (Fig. 4B). The systolic area index, which is the ratio of the right ventricular to the LV systolic pressure-time area on inspiration versus expiration, was 1.3 (>1.1). Based on these findings and the course of treatment for Parkinson's disease, the patient was diagnosed with CP induced by long-term pergolide treatment.

Pergolide was discontinued, and the patient was administered intravenous diuretics; however, his symptoms demonstrated little improvement. Consequently, he became a candidate for surgery, and pericardiectomy was performed. The pericardium was removed almost completely. The histopathological findings of the removed pericardium revealed no malignancy, infection, or tuberculous granuloma. However, thickened fibrotic pericardial tissue and focal inflammation (Fig. 5A, B and C) were found, which was consistent with CP induced by long-term pergolide treatment causing fibrosis reaction.

Postoperatively, the patient's hemodynamics improved substantially. The mean RA pressure decreased (5 mmHg) with no prominent Y descent. The pulmonary artery pressure (28/8 mmHg) and mean pulmonary capillary wedge pressure (8 mmHg) decreased. Simultaneous pressure tracing of the left and right ventricles revealed no dip-and-plateau pattern or ventricular interdependence. The systolic area index decreased to 1.0. Serum levels of N-terminal pro-B-type natriuretic peptide (484 pg/mL) and creatinine (1.48 mg/dL) improved. He now has no leg edema or dyspnea with only a low dose of diuretics (furosemide 20 mg/day) administered in the 1.5 years after surgery. Control of Parkinson's disease has been achieved by increasing the dose of selegiline hy-

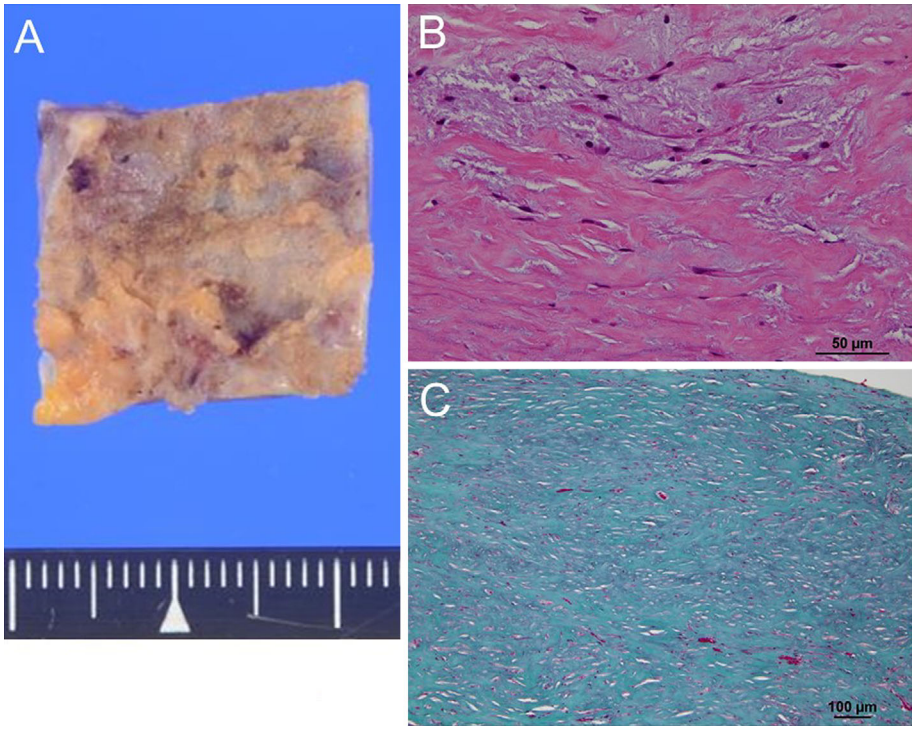

Figure 5. **Histopathological specimens of the removed pericardium revealing thickened fibrotic pericardial tissue (A: pathological macro finding, B: Hematoxylin and Eosin staining, ×400, C: Elastica-Masson stain, ×100).**

drochloride (from 7.5 to 10 mg/day).

Discussion

We herein report the first case of CP induced by long-term pergolide treatment for Parkinson's disease, which was assessed using multimodal imaging.

CP is a chronic inflammatory process often characterized by chronic scarring, fibrosis, and calcification of the pericardium associated with diastolic dysfunction, eventually leading to heart failure. The most frequent causes of CP are idiopathy, post cardiac surgery and previous radiation therapy to the mediastinum in the Western world (1). Although rare, an association between an ergoline-based dopamine receptor agonist, such as pergolide, and CP has been recognized (2, 3). Pergolide may induce fibrotic changes in the lung, pleura, retroperitoneum, and cardiac valve leaflets, which are potentially mediated by the 5-HT2B agonist activity on the serotonergic receptors (4). In the present case, thickening of all of the valve leaflets and pericardium were observed. Although the mechanism underlying CP induced by long-term pergolide with the absence of significant extracardiac lesions remains unclear, pergolide is associated with idiosyncratic fibrotic reactions that may lead to CP, as indicated by the pathological findings of the pericardium in this case.

The findings obtained in our imaging study were not markedly different from those of previous studies on idiopathic CP, postoperative CP, and radiation-induced CP. Although no characteristic findings were found for CP induced by long-term pergolide treatment for Parkinson's disease, there have been no previous reports of a multimodality evaluation, so this fact was a new finding.

CP often mimics other forms of heart failure and requires a specialized work-up; therefore, the diagnosis may be difficult. Meticulous echocardiography allows for the initial detection of dissociation of the intrathoracic and intracardiac pressures and enhanced ventricular interaction, changes that are suggestive of CP. Cardiac CT facilitates the assessment of pericardial thickening and calcification, although neither finding is necessary for a diagnosis. CMR tissue tracking offers additional information, including allowing the identification of pericardial-myocardial adhesions. Cross-sectional imaging and hemodynamic catheterization are necessary to confirm the CP diagnosis.

There are various subtypes of CP. Although rare, there are cases of effusive CP and mixed CP being complicated by myocardial disease, requiring special anti-inflammatory therapy or disease-specific treatment. CMR and PET are useful in differentiating such cases. The use of multimodal imaging has helped to differentiate the subtypes of CP, identify patients who would benefit from medical therapy, and guide pre-operative planning. Thus, the diagnosis of CP requires multimodal imaging (5), as in the present case. It is important to make accurate diagnoses and treatment plans using all imaging modalities available. Complete surgical pericardiectomy remains the only definitive treatment for CP.

This case demonstrates the importance of performing multimodal imaging of CP induced by long-term pergolide treatment for Parkinson's disease. Both the recognition of

pergolide-caused CP and its accurate diagnosis using multimodal imaging will contribute to the early detection and treatment of CP induced by pergolide.

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