Burning chest pain as a prodromal sign in autopsy-proven Parkinson’s disease dementia

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Abstract

Pain is common in Parkinson’s disease (PD) from its early phase. However, there are no reports of autopsy-proven PD dementia with unusual pain. We report the case of a woman with PD dementia who initially presented with unyielding central neuropathic chest pain and parkinsonism. Diagnostic workup showed no abnormal findings related to her pain. Although her parkinsonism was responsive to dopaminergic medication, her clinical status rapidly deteriorated to dementia with hallucinations and delusions over 2 years. An autopsy was performed following death after 6 years of disease. Pathologic examination revealed diffuse Lewy body pathologies (Braak stage VI), limbic-predominant Alzheimer’s disease pathology, and TAR DNA-binding protein 43 pathologies in the amygdala. The patient was an APOE4 carrier. Multiple pathologies concurrent with the APOE4 allele might be associated with rapid clinical deterioration. Although pathologic substrates for pain remain uncertain, the initial presentation of unusual pain merits further clinicopathological correlation studies.

Keywords: Parkinson’s disease; dementia; pain; Lewy body

INTRODUCTION

Parkinson’s disease (PD) diagnostic criteria are based on cardinal motor symptoms and underscore the presence of non-motor symptoms. Non-motor symptoms, including pain, can appear before motor symptom onset. Various types of pain such as musculoskeletal (e.g., shoulder pain) and central neuropathic pain can appear during the early or pre-motor phase of PD, and may be alleviated using dopaminergic medication (“PD-related pain”). Discriminating PD-specific pain from the prevalent pain symptoms of unaffected people is challenging. However, considering the possibility of PD in individuals with unusual painful sensations with bizarre neuropathic or visceral characteristics is helpful in early PD diagnosis. Here, we report a case of autopsy-confirmed PD dementia (PDD), wherein the patient experienced unyielding, unusual chest pain before motor symptom onset.

CASE REPORT

A 60-year-old woman visited our hospital complaining of abnormal sensory discomfort (“My heart and upper back seem to be on fire several times a day”) for three years. Each episode lasted 1–2 hours. Gastrointestinal (GI), cardiac, or respiratory symptoms were absent. She had no other nonmotor symptoms except for depression taking antidepressants (milnacipran 50mg, bupropion 150mg, and clonazepam 0.5mg per day).

Neurological examination revealed hypomimia, monotonous speech, and bilateral bradykinesia and rigidity worse on the left side (Unified PD Rating Scale Part III=17). She had mild depression (Beck Depression Inventory, BDI=8) and mild cognitive impairment (MCI) in the Korean version of the Montreal Cognitive Assessment (MoCA-K=24).

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treatment, but reduced partially with nortriptyline and gabapentin.

At age of 62, she became more depressed (BDI=11) and cognitively impaired (MoCA-K=16). Subsequently, she developed presence hallucinations and persecutory delusions, while her chest pain slightly abated. She experienced severe anxiety and depression and abandoned daily chores. She became increasingly irritable and exhibited offensive behaviors, such as biting her caregivers. Her routine laboratory studies were unremarkable, but cognitive performance had markedly declined (MoCA-K=7). The Neuropsychiatric Inventory Questionnaire identified moderate delusions, hallucinations, dysphoria/depression, aberrant motor behaviors, and nighttime behavioral disturbances (total score=37). The patient’s psychiatric problems were only partially controlled by medication adjustments such as the addition of quetiapine and rivastigmine. She was transferred to a nursing home. At age 65, she died of aspiration pneumonia at a local hospital.

In the postmortem study, gross examination revealed cerebral atrophy with sulcular enlargement and depigmentation of the substantia nigra (SN) and locus coeruleus. Histological analysis showed marked neuronal loss in the SN, where α-synuclein immunostaining confirmed Lewy bodies and/or Lewy neurites, which were widespread, including in the limbic and cortical areas (Braak stage VI) (Figure 1). Immunostaining studies revealed amyloid-β and phosphorylated-tau neurofibrillary tangles in multiple areas, consistent with the pathologic diagnosis of Alzheimer’s disease (AD) (Thal stage 5 [A score=3], Braak stage III [B score=2], CERAD 2 [C score=2]). Cytoplasmic aggregation of TAR-DNA binding protein 43 (TDP-43) was found in the amygdala (limbic-predominant age-related TDP-43 encephalopathy).

(Figure 1. Diffuse Lewy body pathologies, limbic-predominant amyloid pathologies, and TDP-43 pathology in amygdala.)

(A) Hematoxylin and eosin stain (scale bar: 20 µm). (B-F) α-synuclein immunostaining (scale bar: 100 µm). (G-K) β-amyloid immunostaining (scale bar: 200 µm in (G) and (K), 2 mm in (H), 100 µm in (I) and (J)). (L) TDP-43 immunostaining (scale bar: 50 µm).

TDP-43, TAR DNA-binding protein-43; CA, Cornu ammonis; DG, dentate gyrus; CGM, central gray matter.
neuropathological change [LATE-NC] stage 1). The genotype of the APOE gene was ε3/ε4.

**DISCUSSION**

The clinical diagnosis of this patient was PDD based on the early establishment of PD and dementia development two years later. The final pathological diagnosis was Lewy body disease combined with AD and LATE-NC. Her bizarre burning sensation three years before PD-motor symptom onset may have been a prodrome of PD/PDD. Coexisting pathologies, including AD and LATE-NC, may have contributed to the rapid evolution of dementia. Although pain is common in PD, its heterogeneity have resulted in its underestimation as a PD prodrome. Some types of pain that are curbed by dopaminergic medications are considered PD-related, but the classification of pain in PD remains controversial. In this patient, since her pain was unresponsive to dopaminergic medications, it can be classified as central neuropathic pain. Although unexplained non-dystonic oral, abdominal, and genital pain have been previously identified in PD, a prodromal peculiar chest pain has not been reported in autopsy-proven PD/PDD.

A prospective cohort study showed that pre-motor pain was associated with PD-incidence in a dose-dependent manner after adjusting for depression. Although previous studies focused on musculoskeletal/PD-related pain and paid less attention to central neuropathic pain, further studies encompassing various types of pain will contribute toward enlisting pain as a prodrome of PD.

In this case, burning pain in the chest and upper back may be a clinical sign associated with a prodromal upper GI dysfunction in PD. Epigastric pain is a typical manifestation of gastroesophageal reflux, the most common prodromal GI system disorder in PD. In addition, chronic pain in PD patients is significantly associated with GI dysfunction and is likely to be reinforced through a vicious positive feedback loop. The endoscopy was performed to find atrophic gastritis related to H. pylori. Since her pain was not relieved by combination treatment including antibacterial agents, antacids and proton pump inhibitors but partially curved by medications for neuralgic pain, her pain was less likely to be related to gastritis.

Chronic unexplained pain could be associated with cognitive decline. Pain perseveration is common in patients with dementia rather than MCI. In our patient, the pain receded at later follow-ups, denying a close association between her pain and cognitive impairment.

One of the significant limitations of this study is that the autopsy was limited in the brain, leaving pathologic changes in the chest or abdomen unexplored. However, since clinical studies including endoscopy and echocardiography were unremarkable and her pain vanished in later stage, further pathologic studies on the chest and abdomen would be inconclusive. Another limitation is the failure to excavate the pathological substrates for her pain, which was impossible in a single case study. Further clinicopathologic studies in a number of cases are needed to elucidate the relationship between prodromal pain and pathologic substrates.

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**DISCLOSURE**

Ethics: This study was approved by local ethics committee (IRB # 2020-06-030). The autopsy was permitted by his family members and conducted under the approved protocol.

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Conflicts of interest: None

**REFERENCES**


