Vanishing cerebral vasculitis in a patient with Lewy pathology

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Abstract

Immune-mediated mechanisms are involved in the pathogenesis of both cerebral vasculitis and Parkinson's disease (PD, brainstem-predominant Lewy pathology), but the presentation of cerebral vasculitis with comorbid Lewy pathology has not yet been reported. Here we present a case of pathologically confirmed vasculitis in a 73-year-old male patient whose postmortem examination revealed Lewy pathology diagnostic of PD. This case study suggests a comorbidity of cerebral vasculitis and Lewy pathology, as well as potential pathogenic interactions between these two disorders with immune-mediated mechanisms.

Keywords: vasculitis, cerebrovascular disease, Parkinson's disease, Lewy pathology, synucleinopathy, immune pathogenesis

Introduction

Cerebral vasculitis is rare and its cause remains unknown[1–3]. A small percentage of patients with cerebral vasculitis present with stroke or focal symptoms[1]. The disease course and outcome of patients with pathologically confirmed vasculitis may be favorable, and "vanishing" cerebral vasculitis has been occasionally reported[2–3].

Lewy pathology is diagnosed by the presence of Lewy bodies (LB) and Lewy neurites (LN), with α-synuclein immunoreactive neuronal inclusions[4]. Parkinson's disease (PD) is a brainstem-predominant Lewy pathology, and clinically characterized by extrapyramidal motor features. Increasing evidence has suggested that immune-mediated mechanisms have been involved

in the pathogenesis of PD[5–8]. PD associated with cerebral vasculitis has not been reported. Here we present an autopsy study of vanishing vasculitis in the patient with Lewy pathology that is pathologically diagnostic of PD.

Case report

A 73 year-old male presented with dysphasia in February 2014. His past medical history included hypertension, hyperlipidemia, and heavy alcohol use. He had also experienced significant tremor of both hands and right leg for years, but no neurological assessment had been documented. Cranial magnetic resonance imaging (MRI) following computed tomo-
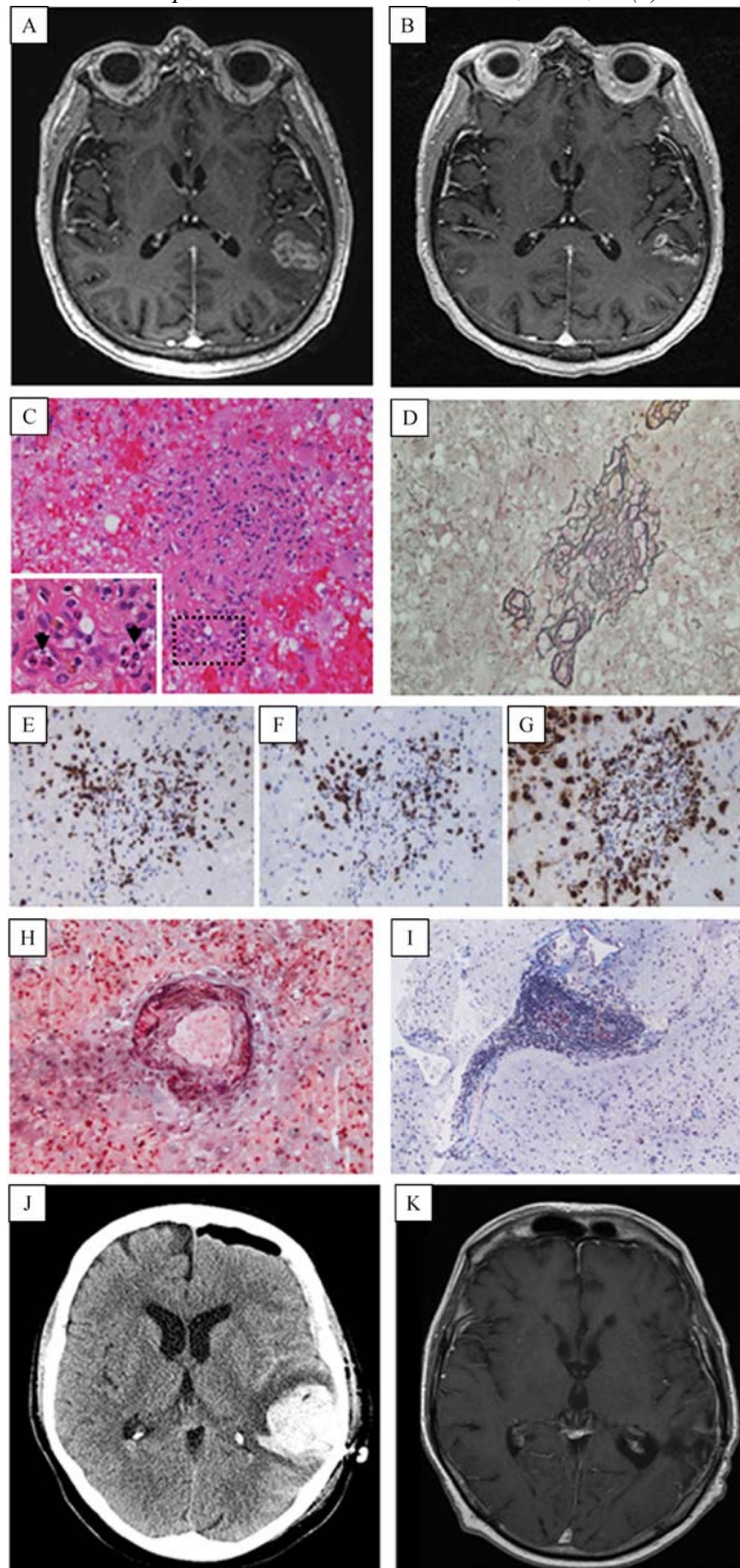
***Fig. 1* Cerebral vasculitis with hemorrhagic infarction.** Post-gadolinium T1-weighted MR images show an ill-defined enhancing lesion in the left temporoparietal lobe 4 weeks prior to the biopsy (A), and decrease in its size one day prior to the biopsy following treatment with corticosteroids (B). Photomicrographs of the lesion in the left posterior temporal biopsy demonstrate an obliterated vessel with the damaged wall and vasculocentric inflammation (C) including focal infiltration of eosinophils (arrows in the inset, and rectangle indicating the area of the inset), and adjacent hemorrhagic infarction (C), reticulin deposition highlighting the damaged vessel wall (D), frequent CD3 + T cells (E), CD8 + cytotoxic T cells (F), and abundant CD68 + macrophages/microglia (G). A blood vessel adjacent to the infarction exhibits transmural inflammation with vessel wall damage (H, Movat stain). Vasculocentric inflammation is also seen along the adjacent leptomeningeal blood vessels (I, Martius Scarlet Blue stain). Original magnification, ×200 (D-H) and ×100 (I). Following the biopsy, a CT image discloses the cerebral hemorrhage adjacent to the operative site (J). A follow-up post-gadolinium T1-weighted MR image 18 weeks after the biopsy demonstrates postoperative changes with minimal enhancement (K).

graphy (CT) disclosed an ill-defined lesion in the left posterior temporoparietal lobe, with hyperintensity on T1-weighted and T2-weighted images, heterogeneous gadolinium enhancement (approximately 2.6×1.6×1.4 cm), tiny hemorrhagic foci, and perilesional edema (*Fig. 1A*). Multifocal tiny T2-weighted hyperintensities were also seen bilaterally in the cerebral white matter. Physical examination revealed moderate aphasia, memory difficulties, a right pronator drift, and bilateral hand tremor. He was treated with corticosteroids. Repeat MRI 4 weeks later demonstrated a decrease in the size of the left temporoparietal lesion (*Fig. 1B*). He underwent a left posterior temporal biopsy in which microscopic examination showed prominent vasculocentric inflammation with transmural infiltration of inflammatory cells and damage to the vessel walls (*Fig. 1C-I*). Infiltrating inflammatory cells were mostly T cells (immunoreactive for CD3, CD4, or CD8), along with occasional eosinophils and infrequent CD20-immunorective B cells. Partial to complete obliteration of the blood vessels was occasionally identified (*Fig. 1C-G*), which was associated with hemorrhagic infarction in the adjacent brain tissue containing more infiltration of CD68-immunoreactive macrophages/microglia. The adjacent leptomeningeal blood vessels were also involved (*Fig. 1I*)[2].

In the evening following the biopsy, CT demonstrated a large cerebral hemorrhage (4.1×3.3×2.3 cm; *Fig. 1J*) adjacent to the operative site. He was then re-operated for evacuation of the hemorrhage. Repeat CTs in the following weeks showed postoperative changes with no new lesions. In late March, he developed bilateral pulmonary emboli and left popliteal deep venous thrombosis, for which he was fully anticoagulated on warfarin. His recovery was complicated by warfarin toxicity, delirium, and difficulty in ambulation. Follow-
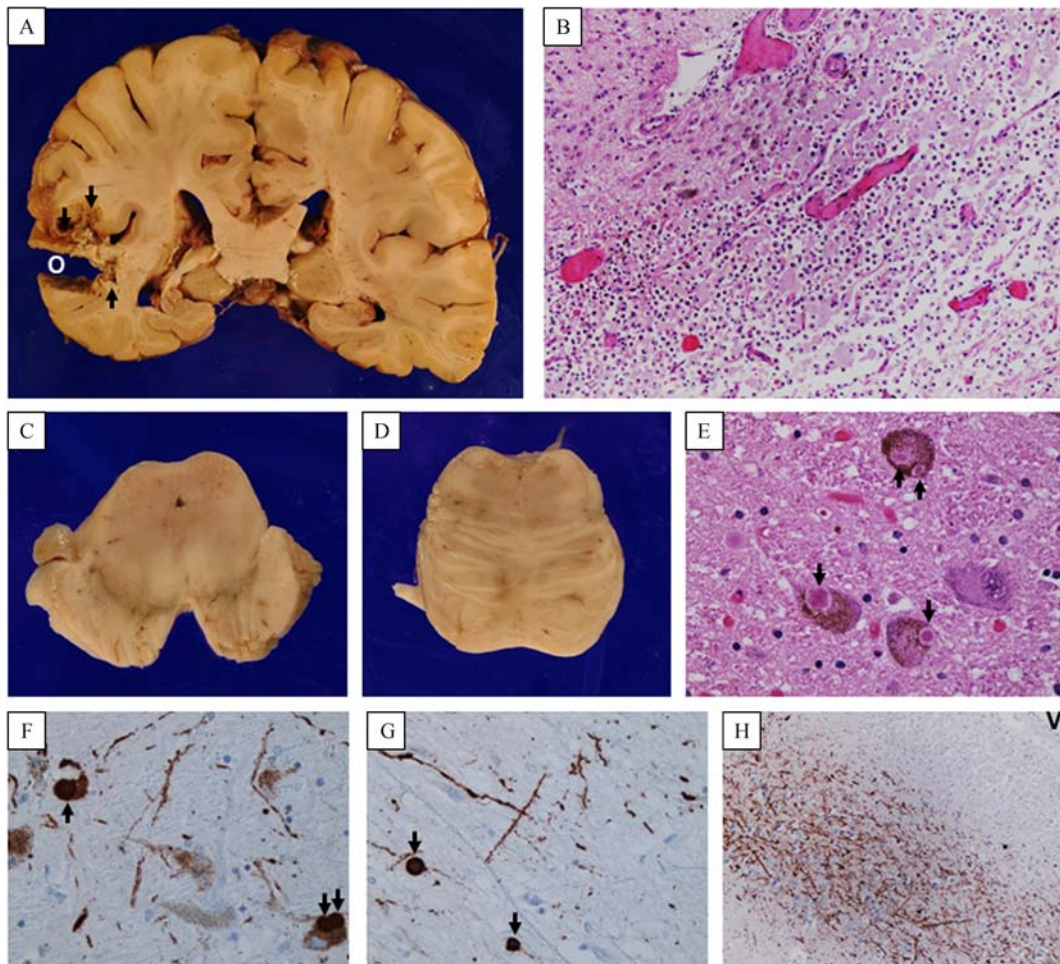

Fig. 2 **Postmortem brain examination.** A coronal section of the brain shows confluent lesions in the posterior temporoparietal lobe, with focal brown discoloration and cavities (A, the defect marked with "O" and some cavities resulted from the premortem operations and a postmortem resection). Microscopic examination on a representative focus reveals chronic hemorrhagic infarction with marked organizing changes including abundant infiltration of foamy macrophages, resulting cavitation, and focal hemosiderin deposition, but minimal lymphocytic infiltration (B). Transverse sections through the midbrain and pons disclose depigmentation of the substantia nigra (C) and locus ceruleus (D). A photomicrograph of the locus ceruleus demonstrates Lewy bodies in the remaining neurons (E, arrows). α-Synuclein immunostaining exhibits positive Lewy bodies and Lewy neurites in the substantia nigra (F), intralaminar thalamic nuclei (G), and cornu ammonis 2 region of the hippocampus (H, "v" at the corner indicating the ventricle). Original magnification, ×100 (B and H) and ×400 (E-G).

up MRIs in April and July (***Fig. 1K***) demonstrated minimal enhancement other than postoperative changes, and CT in September showed no pathological enhancement. He received palliative care at the local hospital, and died of bronchopneumonia in November 2014.

A general autopsy confirmed bilateral bronchopneumonia, but no evidence of systemic vasculitis. The brain weighed 1,290 g. Its gross examination disclosed confluent lesions with focal cavitation and brown discoloration in the left temporoparietal lobe (***Fig. 2A***). Microscopic examination showed chronic hemorrhagic infarction and/or hemorrhage in the left temporoparietal lobe, with focal cavitation, hemosiderin deposition, and extensive infiltration of macrophages (***Fig. 2B***). Minimal brain atrophy was seen. Transverse sections of the brainstem exhibited mild to moderate depigmentation of the substantia nigra (SN, ***Fig. 2C***) and locus ceruleus (LC; ***Fig. 2D***). The adjacent tissue exhibited markedly reactive changes. Wallerian degeneration of the left pyramidal tracts was noted. However, there was no active vasculitis.

The brain was also remarkable for Lewy pathology. The loss of pigmented neurons in SN and LC was microscopically moderate (***Fig. 2C-F***). LB was readily found in the brainstem nuclei including LC and SN. α-Synuclein immunostaining demonstrated LB and LN frequently in the brainstem nuclei, intralaminar thalamic nuclei (***Fig. 2G***), and cornu ammonis 2 region of the hippocampus (***Fig. 2H***), but occasionally in the transentorhinal region and rarely in the neocortex. There was no evidence of cerebral amyloid angiopathy or other neurodegenerative diseases other than age-related changes. This brain Lewy pathology corresponds to the pathological stage 4 (out of 6) for PD[4].

Discussion

The present case is the first to demonstrate vanishing vasculitis in a brain with Lewy pathology. The postmortem neuropathological findings are diagnostic of PD, which may explain the late-disclosed tremor in this patient.

PD produces some compromise in immune cells with dysregulated inflammatory responses. In PD, activation of the innate and adaptive immune system has been known to accompany the neuronal death[4–6]. The changes in numbers and some receptors of lymphocytes, particularly T cells, have been noted in the animal model of PD[6] and patients with PD[7–8]. In our present case, the immune pathogenic process of Lewy pathology is likely interacting with that of vasculitis.

Cerebral vasculitis can be caused by different pathogenic mechanisms[1–3]. Immune-mediated mechanisms are well-known, in which both macrophages and T cells are involved to contribute to the vessel damage. In our present case, the vanishing course of vasculitis may be attributable to the treatment with corticosteroids and/or its complex interactions with CVD-induced macrophage infiltration and immune-mediated mechanisms of Lewy pathology. The pathogenic relationship between cerebral vasculitis and Lewy pathology deserves further investigation.

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