Perivasculitic Panencephalitis with Relapsing Polychondritis: An Autopsy Case Report and Review of Previous Cases

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Abstract

We herein report an autopsy case of relapsing polychondritis encephalitis coexisting with a Lewy body pathology and also review previous autopsy cases. A 59-year-old man exhibited a tremor of the right hand, small-steppage gait and bradykinesia. Five years later, he presented with relapsing auricular chondritis and scleritis and subsequently showed exacerbation of extrapyramidal symptoms. A histological examination revealed perivasculary lymphocytic cuffing and infiltration in the small vessels, as well as loss of nerve cells and gliosis in the basal ganglia, insular gyrus and medial temporal lobe. The present case was characterized by perivasculitic panencephalitis and the coexistence of a Lewy body pathology, which may have augmented the patient’s parkinsonism.

Key words: relapsing polychondritis, perivasculitic panencephalitis, Parkinson’s disease, basal ganglia, autopsy, neuropathological examination

Introduction

Initially described in 1923 by Jaksch-Wartenhorst (1), relapsing polychondritis (RP) is a rare autoimmune disorder characterized by the recurrent inflammation of cartilage throughout the body, including the auricular, nasal, tracheobronchial, valvular and articular cartilage (2). The disease can also involve other proteoglycan-rich structures, such as the eyes, heart, blood vessels, inner ears and kidneys (3). The neurologic complications of RP have received little attention, and RP may follow a fluctuating course that challenges the differential diagnosis (4). We herein present an autopsy case of RP encephalitis complicated by Parkinson’s disease (PD), with a review of previous autopsy cases and also a discussion of RP and RP encephalitis.

Case Report

A 59-year-old Japanese man developed a tremor of the right hand. At 60 years of age, the tremor of the right hand progressed in addition to the development of small-steppage gait and bradykinesia. He was subsequently diagnosed with PD and began to receive oral drug therapy, with symptomatic relief. Two years later, his symptoms gradually worsened. Brain magnetic resonance imaging (MRI) showed no abnormalities, including in the basal ganglia and substantia nigra.

At 64 years of age, six months before the current admission, the patient repeatedly presented with bilateral ear swelling and pain, which were treated with steroid ointment. He developed scleritis in the right eye two weeks later, followed by scleritis in the left eye two months later, and was treated with steroid eye drops. One month prior to admission, his gait disturbance worsened. A computed tomographic scan of
was 36.5°C, and both ears were swollen and deformed (Fig. 1b). A neurological examination showed a mild consciousness disturbance, obscure speech, disorientation and attention deficits. Lead-pipe rigidity was noted in the right limbs, and a resting tremor was observed in the right hand and bilateral feet.

Laboratory blood tests revealed an inflammatory reaction, including an increased leukocyte count of 12,800/mm³ and a C-reactive protein level of 2.3 mg/dL. Other laboratory parameters were within the normal ranges. Serum autoantibodies and antiviral antibodies were negative. The CSF was normal, and various CSF antiviral antibodies and polymerase chain reaction DNA for the herpes simplex virus were negative. Neither the serum and CSF anti-glutamate receptor (GluR) ε2, -N-methyl-D-aspartate receptor nor -neutral glycosphingolipid autoantibodies were examined. On brain MRI, which was performed on the third day of admission, the swelling and hyperintensity on T2-weighted and FLAIR images had slightly improved. Two weeks after admission, a biopsy of the right ear cartilage showed fibrosis and degeneration (Fig. 1c), suggesting relapsing polychondritis. Left elbow joint MRI demonstrated abnormal synovial fluid collection and edema in the periarticular soft tissue.

Based on these findings, we diagnosed the patient with encephalitis associated with RP. The intravenous injection of 500 mg/day of methylprednisolone for three days again improved his symptoms, followed by oral prednisolone at a dose of 50 mg/day for four weeks, which was then tapered gradually to 5 mg/day. One month later, the patient’s neurological symptoms and serological data were almost normal, and he was transferred to another hospital for palliative care. One month later, he died due to pneumonia. A brain autopsy was performed immediately after his death.

**Neuropathological findings**

The weight of the brain was 1,280 g before fixation, and no arachnoidal opacity was observed. The right temporal lobe was atrophic compared to the left side, and the right inferior horn was mildly dilated. Depigmentation of the substantia nigra and locus coeruleus was evident; however, these structures appeared otherwise normal macroscopically (figure not shown). The spinal cord was not examined.

A histological examination revealed perivascular lymphocytic cuffing and infiltration in the small arteries and veins as well as the severe loss of nerve cells and gliosis in the right basal ganglia, insular gyrus and medial temporal lobe, including the hippocampus and parahippocampal gyrus (Fig. 2a). Several perivascular lymphocytes had also infiltrated the vascular walls, suggesting diffuse vasculitis. Small focal necrosis in the right hippocampus and parahippocampal gyrus appeared to include dead inflammatory lesions. Foci of milder neuronal loss and gliosis were distributed in the bilateral basal ganglia, medial temporal lobe, frontal lobe, thalamus and medulla oblongata (collectively indicated by dots in Fig. 2b-d). There were almost no senile plaques, and few neurofibrillary tangles were observed. In the bilateral substantia nigra and locus coeruleus, there were diffuse

![Figure 1](https://example.com/image1.png)

**Figure 1.** (a) Brain MRI performed on the fifth day after admission showing high signal intensity in the right putamen and limbic cortex, including the insula, temporal cortex and frontal cortex, on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. (b) A photograph showing the patient’s right ear to be swollen and deformed. (c) A photomicrograph showing the histopathology of the right ear cartilage with fibrosis and degeneration (magnification: x40).

Initially, the patient exhibited an intermittent high fever and rapid worsening of parkinsonism, including akinesia, rigidity in all extremities and gait disturbance. The levels of serum tumor markers, autoantibodies and antiviral antibodies showed no significant abnormalities. The cerebrospinal fluid (CSF) was sterile, with an increased cell count of 25/mm³ (lymphocyte dominant) and increased protein level of 87 mg/dL. Brain MRI performed on the fifth day after admission revealed swelling and high signal intensity in the right putamen and limbic cortex, including the insula, on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1a). The patient was treated with antibiotics and antiviral drugs; however, no beneficial effects were observed. He showed a transient improvement in his symptoms after he was started on intravenous steroid therapy; however, the symptoms subsequently worsened again. He was therefore transferred to our hospital for a further investigation.

On a physical examination, the patient’s body temperature was 36.5°C, and both ears were swollen and deformed...
Lewy bodies with the mild loss of pigmented nerve cells. There was no severe inflammation or neurophagocytosis. In addition, there were no multinucleated giant cells or neurons and glial cells with intranuclear or intracytoplasmic inclusion bodies.

Discussion

The present patient presented with encephalitis characterized by a high fever, consciousness disturbance and rapidly worsened akinesia, with rigidity of all extremities and a gait disturbance during the course of PD. Brain MRI showed lesions in the right basal ganglia, medial surface of the frontal lobe and limbic cortices. The patient exhibited scleritis, inflammatory arthritis and recurrent chondritis in both ears, and a biopsy confirmed fibrosis and inflammation. The diagnosis of RP was established based on these clinical features according to the criteria proposed by McAdam et al. (2) and the modified version proposed by Damiani and Levine (5). The symptoms in the present case were insufficient for the former, although they fulfilled the latter.

The incidence of PD is 100-150 of every 100,000 persons, while that of RP is several of every 100,000 persons. To our knowledge, there are no case reports of RP encephalitis complicated with PD. As a result, the present report is thus considered to be the first neuropathological report of this feature. Previously, three cases with RP encephalitis presenting with parkinsonism have been reported. Defer et al. (4) reported the case of a 67-year-old man who presented with a two-month history of parkinsonism, including plastic rigidity and limb and axial hypokinesia. Fujioka et al. (6) reported the case of a 66-year-old woman who presented with a two-week history of slowness of movement and difficulty walking. Meanwhile, Head et al. (7) reported an autopsy case, as shown in the Table. In addition, a few previous patients have shown partial or mild extrapyramidal symptoms possibly attributable to vasculitis or encephalitis extending to the basal ganglia.

We considered the patient’s central nervous system (CNS) signs and symptoms and MRI findings to be derived from RP encephalitis. Initially, his symptoms of PD appeared to worsen as a natural course; however, our subsequent observations of his ear and eye symptoms led us to the correct diagnosis. It is of clinical relevance to make the differential diagnosis based on physiological and radiological findings. In the present case, it was particularly important to exclude a diagnosis of viral encephalitis. The patient had no physiological symptoms, such as signs of meningeal irritation. The increased cell count in the CSF was not as high as that observed in patients with common viral encephalitis, and the
The present patient showed an improvement in his symptoms following treatment with steroid therapy, but not antiviral drugs.

Respiratory tract involvement is a relatively unusual feature of RP. However, this characteristic is noteworthy, as it may represent critical and potentially lethal organ system involvement (2). The present patient died of pneumonia, although he did not show any airway involvement. In a nationwide epidemiologic survey of RP in Japan, patients with airway involvement who were treated with corticosteroid monotherapy invariably required tracheotomy, suggesting that the effect of corticosteroid monotherapy is insufficient to prevent the progression of airway disease (8). Therefore, it is necessary to pay adequate attention to the possibility of airway involvement when treating RP. Moreover, in previous reports, the administration of early steroid therapy and additional immunosuppressive agents may have improved the patient outcomes, although the response to these treatments are not consistent, and relapse of encephalitis or brain atrophy have also been reported (3, 9).

The auricular cartilage contains large amounts of neutral glycosphingolipids (10), and patients with RP exhibit marked auricular inflammation and induration. Mihara et al. (11) speculated that the presence of abundant neutral glycosphingolipids induces an autoimmune response. Meanwhile, Kashihara et al. (12) reported the case of an anti-GluRε2 (NR2B) autoantibody-positive patient with limbic encephalitis associated with RP. Unfortunately, the present patient was not examined for anti-neutral glycosphingolipid antibodies or anti-GluRe2 autoantibodies.

There have been only six autopsy case reports describing the detailed neuropathological findings of CNS involvement in patient with RP (Table), possibly because RP is a rare disorder that is responsive to steroid therapy. Stewart et al. (13) reported extensive cerebral and systemic vasculitis to be the cause of CNS involvement in patient with RP. In contrast, other authors have reported inflammatory changes not specific to vessels in patients presenting with limbic encephalitis or meningoencephalitis associated RP (7, 14-17). In these autopsy cases, diffuse vasculitis and/or perivascular infiltration were observed, with gliosis in the leptomeninges and brain parenchyma of the limbic area and basal ganglia, etc. The present patient exhibited essentially similar features to the aforementioned findings; i.e., perivascular lymphocytic cuffing and infiltration in small vessels, with a loss of nerve cells and gliosis in the basal ganglia, insular gyrus and medial temporal lobe.

The current patient presented with a five-year history of tremors, a gait disturbance and bradykinesia with a predominance on the right side. However, lesions of RP encephalitis were predominant in the right basal ganglia, namely, the wrong side for parkinsonism. Therefore, the final neuropathological diagnosis was RP encephalitis complicated by PD. It is highly likely that the incidental RP lesions in the basal ganglia worsened the patient’s parkinsonism during the course of PD.

### Table. Reports of Autopsy Cases with Encephalitis of Relapsing Polychondritis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Presenting symptoms</th>
<th>Neuropathological change</th>
<th>Main sites of pathological lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>71/M</td>
<td>EPS, cognitive impairment, psychiatric symptoms</td>
<td>Severe nerve cell loss within the hippocampus, entorhinal cortex and amygdala that was associated with patchy but widespread lymphocytic infiltration, predominantly within the leptomeninges.</td>
<td>Meningoencephalitis, vasculitis</td>
</tr>
<tr>
<td>13</td>
<td>57/M</td>
<td>Delirium, reduced visual acuity, stiff neck</td>
<td>Diffuse vasculitis, involving medial and smaller arteries and small veins in at least 60%, Some perivascular areas with large numbers of lymphocytes and molecular cells with or without plasma cells. Areas of true necrotizing vasculitis, some being 10 times thicker than their lumina.</td>
<td>Cerebral vasculitis</td>
</tr>
<tr>
<td>14</td>
<td>53/M</td>
<td>Cognitive impairment, change in behavior, slow psychomotor speed</td>
<td>Neuronal loss, gliosis and microglial nodules in the hippocampus, cingulate gyrus, temporal and occipital lobes. Patchy perivascular cuffing, and leptomeningeal lymphocytic infiltrates in the cerebral cortex, striatum, thalamus and medulla.</td>
<td>Limbic/panencephalitis</td>
</tr>
<tr>
<td>15</td>
<td>56/M</td>
<td>Emotional lability, speech latency, myoclonus</td>
<td>Infiltration of the meninges, brain cortex by T-cells with an abundance of activated microglia. No evidence of vasculitis.</td>
<td>Meningoencephalitis</td>
</tr>
<tr>
<td>16</td>
<td>76/F</td>
<td>Decreased spontaneous speech, volunatry behavior</td>
<td>Perivascular lymphocyte infiltration in the pia mater and the cerebrum white matter, and inflammatory destruction of the myelin sheath.</td>
<td>Perivasculitic meningoencephalitis</td>
</tr>
<tr>
<td>17</td>
<td>73/M</td>
<td>Confusion, disorientation</td>
<td>Nonspecific subacute and chronic inflammation of the meninges and both white and grey matter, affecting temporal lobe, hippocampus, the visual cortex, basal ganglia and thalamus.</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Current patient</td>
<td>64/M</td>
<td>EPS, lowering of consciousness</td>
<td>Perivasicular lymphocytic cuffing and infiltration of small vessels, loss of nerve cells and gliosis in the basal ganglia, insular gyrus and medial temporal lobe.</td>
<td>Perivasculitic panencephalitis</td>
</tr>
</tbody>
</table>

EPS: Extrapyramidal symptoms
The authors state that they have no Conflict of Interest (COI).

References