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Relapsing polychondritis with features of dementia with Lewy bodies

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Abstract We describe a 72-year old man with clinical features suggestive of dementia with Lewy bodies (DLB) who proved neuropathologically to have degeneration induced by relapsing polychondritis (RP), an autoimmune inflammatory disorder of cartilaginous tissues. There was lymphocytic infiltration of the leptomeninges, perivascular cuffing, reactive astrocytosis, and activation of microglia in multiple brain areas all consistent with an immunologically mediated process. There was widespread neuronal loss within the hippocampus, entorhinal cortex, and amygdala as well as diffuse myelin pallor of cortical pathways. Elevated levels of complement proteins and endothelial markers of inflammation were observed, which are similar to previous reports in DLB. This study demonstrates that qualitatively similar inflammation-associated neurodegeneration is present in widespread regions of the brain in a RP case presenting clinically as DLB.

Keywords Complement · Hippocampal cell loss · Neuroinflammation · White matter degeneration

Introduction

Initially described in 1923 by Jaksch-Wartenhorst [23], relapsing polychondritis (RP) is an autoimmune disorder affecting connective tissues and most commonly leads to inflammation-induced deformity of the ear or nasal cartilage [31, 33, 49, 52]. However, clinical disease at other sites is common and may include arthritis or pulmonary, renal, dermatologic, cardiovascular, or neurologic manifestations [24]. Typically RP is diagnosed on the basis of clinical signs [31], and 33–50% of patients develop autoantibodies against type II collagen [12] and, less frequently, against collagen IX and XI, and matrilin-1 [16]. Tissue pathology typically includes infiltration by T lymphocytes and plasma cells and accumulation of granular deposits of immunoglobulins and complement, suggesting the presence of immune complexes [16, 49]. RP is frequently associated with other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, progressive systemic sclerosis, and other rare connective tissue diseases [33]. On the other hand, inflammation has been considered to be a possible contributing factor in the development of neurodegeneration in a variety of dementing disorders [1].

We describe a 72-year old man with RP who died after a 3-year illness characterized by clinical features suggestive of dementia with Lewy bodies (DLB). He did not respond to anticholinesterase or dopaminergic agents and refused corticosteroid therapy. The dementia was marked by a fluctuating course, recurrent visual

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hallucinations, and parkinsonism [32]. Neuropathologically, he proved to have neither DLB nor Alzheimer disease (AD) but, instead, showed multifocal, predominantly leptomeningeal infiltration by inflammatory cells and brain degeneration that we believe was immunologically mediated and associated with the RP that he suffered from during life.

Case report

A right-handed, 71-year old Caucasian male with 14 years of education presented at the University of California, Irvine–Alzheimer’s Disease Research Center (UCI-ADRC) in early November 2001 with complaints of memory loss, language difficulties, abnormal motor behavior, and visual hallucinations as well as depression, agitation, and insomnia. His family history was significant for memory problems for both his mother (died at 95 years of age) and his father (died at 82 years of age) but the cause of these difficulties was not established. His siblings did not show signs of dementia and both were deceased (sister age 74 and brother age 68 years). According to his wife, he was in good health until April 2000, at the age of 69 years, when he became acutely vertiginous immediately after colonoscopy. The family reported that dizziness and balance problems persisted and evolved to include other symptoms, including forgetfulness, tremor, and pains in the lower extremities. A neurological examination in November 2000 was interpreted as normal, with no sensory, motor, or gait abnormalities. Within a few months there were rapid shifts in both mood and other cognitive fluctuations including orientation, recent memory, and recognizing familiar locations (e.g., houses on his street).

Fourteen months later the patient had a motor vehicle accident after becoming confused and failing to stop the car. A CT scan of the brain performed immediately following the accident revealed global atrophy and two small bilateral frontal subdural hygromas, which were thought to not be significant contributing factors to his cognitive decline. The right ear was noted to be swollen with tissue hemorrhages. The mini-mental status examination (MMSE [13]) score was in the moderately demented range (17/30). He was started on Aricept (Donepezil) but continued to decline mentally. In April 2001 he developed daily visual hallucinations (bugs and bright lights), and on occasion, “visions of bad people killing people” that subsequently became less frequent and eventually disappeared. A SPECT scan performed near the end of April 2001 showed significant cortical atrophy with decreased perfusion within cortical grey matter, particularly in the left occipital–parietal region.

In June 2001, motor and language impairments developed. The spouse reported that he was depressed and that he would frequently fall. On examination he expressed concern about these changes, had few spontaneous movements, maintained a fixed “smile” and blinked only occasionally. His speech was marked by paraphrasias and perseverations. He was unable to spell and his writing was slowed and incomprehensible. The cranial nerve examination showed absence of upward gaze. When he was asked to move his arms, a rhythmic tremor appeared accompanied by sudden irregular brief jerks consistent with myoclonus. His gait was stiff without associated arm movements but was not festinating nor was cogwheeling observed on testing muscle tone in the arms. Tendon reflexes were hypoactive and the plantar responses were flexor. There were bilateral grasp responses present. He demonstrated fixed dystonic posturing of the arms. Motor and reflex abnormalities were consistent with both frontal and extrapyramidal motor disorders. Sinemet (25–50 mg bid) was administered without benefit. The findings of dementia accompanied by extrapyramidal signs (slowness of movement, tremors, repeated falls) and unresponsive to Sinemet suggested a diagnosis of DLB. Bilateral deformities of the auricles consistent with RP were also noted (Fig. 1), but biopsy of the ear for confirmation of the diagnosis was refused.

The cognitive disorder progressed and 3 months later, he had to be evaluated using the severe impairment battery (SIB [37]) where his score was 73/100. The patient’s lowest scores occurred on tasks involving praxis, orientation, language, and recent memory, while visual-spatial and constructional skills remained relatively preserved. Neurological signs had worsened to include a bilateral resting tremor, bradykinesia, bilateral cogwheeling, and abnormal postural balance. Bilateral myoclonus and gait impairments were also observed.

His rapidly progressive dementia, fluctuating course, visual hallucinations, and extrapyramidal motor signs were thought to be consistent with a diagnosis of possible DLB. Table 1 summarizes features suggestive of DLB according to the criteria of McKeith et al. [32]. Three years after the onset of cognitive dysfunction and 8 months after his last neuropsychological evaluation, he died of pneumonia.

Materials and methods

Brain tissue procedure

The brain, which was collected within 3.6 h of death, was sectioned through the midline. The right cerebral



Fig. 1 Photograph of the patient illustrating inflammation of the cartilage of the ear, which is a feature of relapsing polychondritis

hemisphere (together with the brainstem and cerebellum) was fixed in 4% paraformaldehyde for 2 weeks, and the left was coronally sectioned and frozen at -80°C after the hippocampus and middle frontal gyrus were first dissected and placed in fixative. Blocks of fixed tissue were embedded in paraffin and sectioned at $8\ \mu\text{m}$. For experimental studies, tissue blocks containing middle frontal gyrus and hippocampus were placed in phosphate buffered saline (pH 7.5) containing 0.02% sodium azide and sectioned with a vibratome at $50\ \mu\text{m}$ intervals.

Histological and immunohistological procedures

Modified Bielschowsky, hematoxylin-eosin, and Klüver–Barrera stains and immunostains for tau, α -synuclein, ubiquitin, glial fibrillary acidic protein (GFAP), and CD68 were applied (Table 2). In thicker $50\ \mu\text{m}$ thick sections, a battery of markers for inflammation, also listed in Table 2, was used. In addition, markers for

Table 1 Comparison of a patient with relapsing polychondritis with clinical criteria for possible or probable DLB [32]

DLB clinical feature	Type of feature	Present	Absent
Cognitive fluctuations	C	✓	
Early visual hallucinations	C	✓	
Early parkinsonian features	C	✓	
Delusions	S		✓
Depression	S	✓	
Minimal or absent response to levodopa	S	✓	
Neuroleptic sensitivity	S		✓
Repeated falls/postural imbalance	S	✓	
Syncope	S		✓
Transient loss of consciousness	S		✓
Hallucinations in other modalities	S		✓
REM sleep behavior disorder	S		✓

Note: C = Core DLB feature; S = Supportive DLB feature

Probable DLB = Dementia plus two or more (C) core features

Possible DLB = Dementia plus one of the core (C) features

Supportive (S) features may aid diagnosis

B-cell, T-cell, and complement proteins were used to characterize the type and extent of inflammation. Standard immunohistochemical procedures were used [19]. Control experiments included elimination of primary or secondary antibodies, which all were negative.

Results

Neuropathology

The brain at autopsy weighed 1,271 g. As seen in coronal section, there was striking atrophy of the temporal lobe, with prominent widening of the sylvian fissure, enlargement of the temporal horn of the lateral ventricle, and shrinkage of the hippocampus (Fig. 2).

Microscopically, neuritic plaque formation was absent within most of the cerebral neocortex, hippocampus, and amygdala; it was observed in mild to moderate degree only within the calcarine/pericalcarine and transentorhinal cortex. Neurofibrillary degeneration, which was judged overall to be of stage I severity by Braak and Braak criteria, was absent at all of the aforementioned sites except for the transentorhinal region, where it was present in trace amounts. According to NIA/Reagan criteria, therefore, the likelihood that dementia was due to Alzheimer disease was low [10].

Table 2 Antibodies used in immunohistochemical experiments

	Antibody	Marker	Host	Source
Complement pathway	C1q	Classical complement pathway	Polyclonal	Dako, Temcula, CA
	C4d	Classical complement pathway	Monoclonal	Quidel Corp., San Deigo, CA
Effector enzymes	C3b	Alternative pathway	Monoclonal	Quidel Corp., San Deigo, CA
	iNOS	Inducible Nitric oxide synthase	Polyclonal	Chemicon International, Temecula, CA
Lymphocytes	CD3	T-lymphocytes	Monoclonal	Novocastra Laboratories, Ltd., UK
	CD4	T-lymphocytes	Monoclonal	Novocastra Laboratories, Ltd., UK
	CD8	T-lymphocytes	Monoclonal	Novocastra Laboratories, Ltd., UK
	CD40	B-cells	Monoclonal	Novocastra Laboratories, Ltd., UK
Gliosis	Anti-GFAP	Astrocytosis	Polyclonal	Dako, Temecula, CA
	LN-3	Microglial activation	Monoclonal	ICN Biomedicals, Aurora, Ohio
AD pathology	6E10	Senile plaques	Monoclonal	Signet Laboratories, Dedham, MA
	AT8	Neurofibrillary tangles	Monoclonal	Pierce Biotechnology, Rockford, IL
Markers used for final neuropathology diagnosis	Anti-ubiquitin	Lewy bodies	Polyclonal	Dako, Temecula, CA
	Alpha-synuclein	Lewy bodies	Polyclonal	Chemicon International, Temecula, CA
	Anti-beta-amyloid	Senile plaques	Monoclonal	Dako, Temecula, CA
	Anti-tau	Neurofibrillary tangles	Polyclonal	Dako, Temecula, CA
	CD68	Microglial activation	Monoclonal	Dako, Temecula, CA

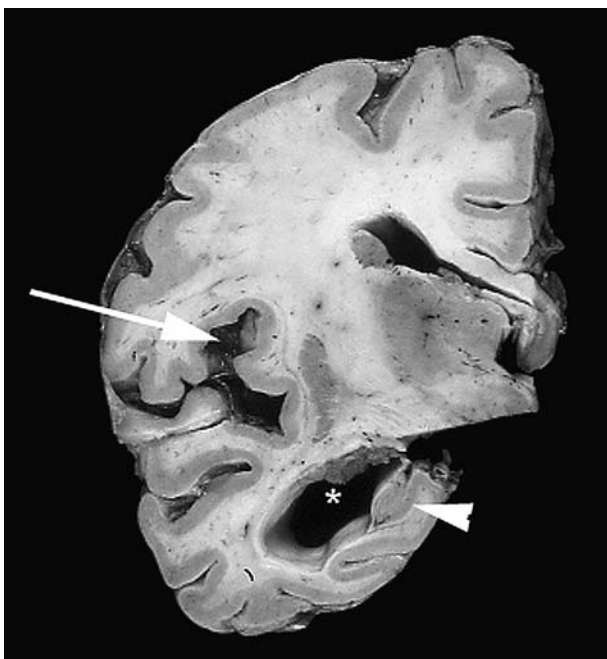
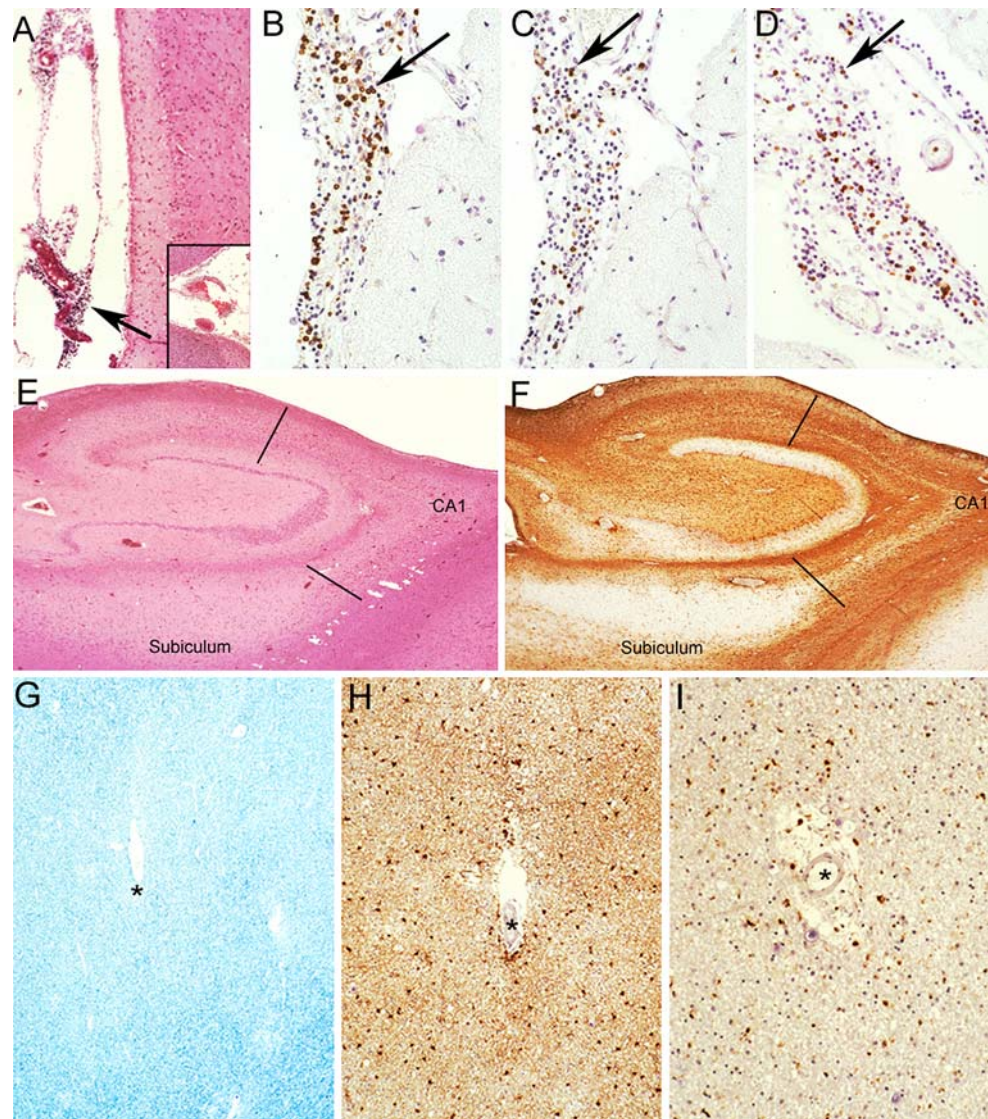


Fig. 2 Photograph of a coronal section showing striking atrophy of the temporal lobe, with prominent widening of the sylvian fissure (*arrow*), enlargement of the temporal horn of the lateral ventricle (*asterisk*), and shrinkage of the hippocampus (*arrowhead*)

The concentration of neuromelanin-bearing neurons within the substantia nigra and locus ceruleus was only mildly reduced, with only minimal amounts of extra-neuronal neuromelanin and with no evidence of neurofibrillary degeneration or Lewy body formation. Lewy bodies and Lewy neurites were also absent from the dorsal motor nucleus of the vagus, amygdala, substantia innominata, hippocampal pyramidal layer, subiculum, entorhinal/transentorhinal region, and rostral cingulate and temporal neocortex.

Mild patchy but widely distributed foci of leptomeningeal infiltration by CD4- and CD8-immunoreactive lymphocytes were observed that occasionally extended into the walls of veins (Fig. 3a). Frank vasculitis was also occasionally encountered (Fig. 3a, inset). CD68-immunoreactive macrophages were also moderately abundant (Fig. 3d) and could be seen in places to extend for short distances into perivascular Virchow–Robin spaces. Subpial reactive astrocytosis and microvacuolar degeneration within layer two were observed in patchy distribution within frontal, temporal, caudal cingulate, and entorhinal cortex. Severe nerve cell loss and reactive astrocytosis were noted within the hippocampal pyramidal layer [especially within CA1 and CA3, with striking sparing of the subiculum (Fig. 3f)],

Fig. 3 Inflammation and selective neuronal loss in the hippocampus. The right hemisphere revealed extensive lymphocyte accumulation associated with the leptomeninges observed with H&E (including vasculitis-inset) (a), anti-CD4 (b), anti-CD8 (c) immunostaining (lymphocytes indicated by arrows). In addition, macrophages were also observed as indicated by arrows (d). Low power photographs of the hippocampus showing extensive pyramidal cell loss in area CA1 (bounded by lines) with the subiculum remaining intact (e). The same area of CA1 also showed extensive astrocytosis (f). In the white matter of the mid-frontal cortex, Klüver–Barra histology revealed white matter pallor and possible vasculitis in areas surrounding large blood vessels as indicated by an asterisk (g). In addition, astrocytosis (h) and microgliosis (i) were also severe in these same regions of pallor



entorhinal cortex, and amygdala. Diffuse loss of myelinated axons, reactive astrocytosis, and proliferation of microglial cells were observed (Fig. 3g–i, respectively), particularly within those regions adjoining sites of severe damage to grey matter.

Glial activation and complement protein immunohistochemistry

Hippocampus

Immunostaining of the left hippocampus for MHC-Class II (LN-3; Fig. 4a), glial acidic fibrillary protein (GFAP) (Fig. 4b), and C1q (Fig. 4c), the first component of the classical pathway complement cascade, revealed extensive glial activation along with significant neuronal labeling for C1q. In addition, immunostaining for another complement factor, C4d, was extensive

within both neurons and blood vessels (Fig. 4d). C4d immunoreactivity appeared as a diffuse cloud of staining in white matter of the hippocampus and, in particular, within the outer molecular layer of the dentate gyrus (Fig. 4f) suggesting an association with entorhinal cortex neuron terminals. iNOS immunolabeling revealed blood vessel labeling (Fig. 4e).

Frontal cortex

Immunostaining of the left frontal cortex showed gliosis that was as extensive as observed in the hippocampus (Fig. 4g, h). C1q immunoreactivity was limited to light diffuse staining with neurons remaining immunonegative for C1q (Fig. 4i). C4d immunostains showed extensive white matter labeling (Fig. 4j). iNOS immunoreactivity was observed in association with blood vessels in the frontal cortex, as it was in the hippocampus (Fig. 4k).

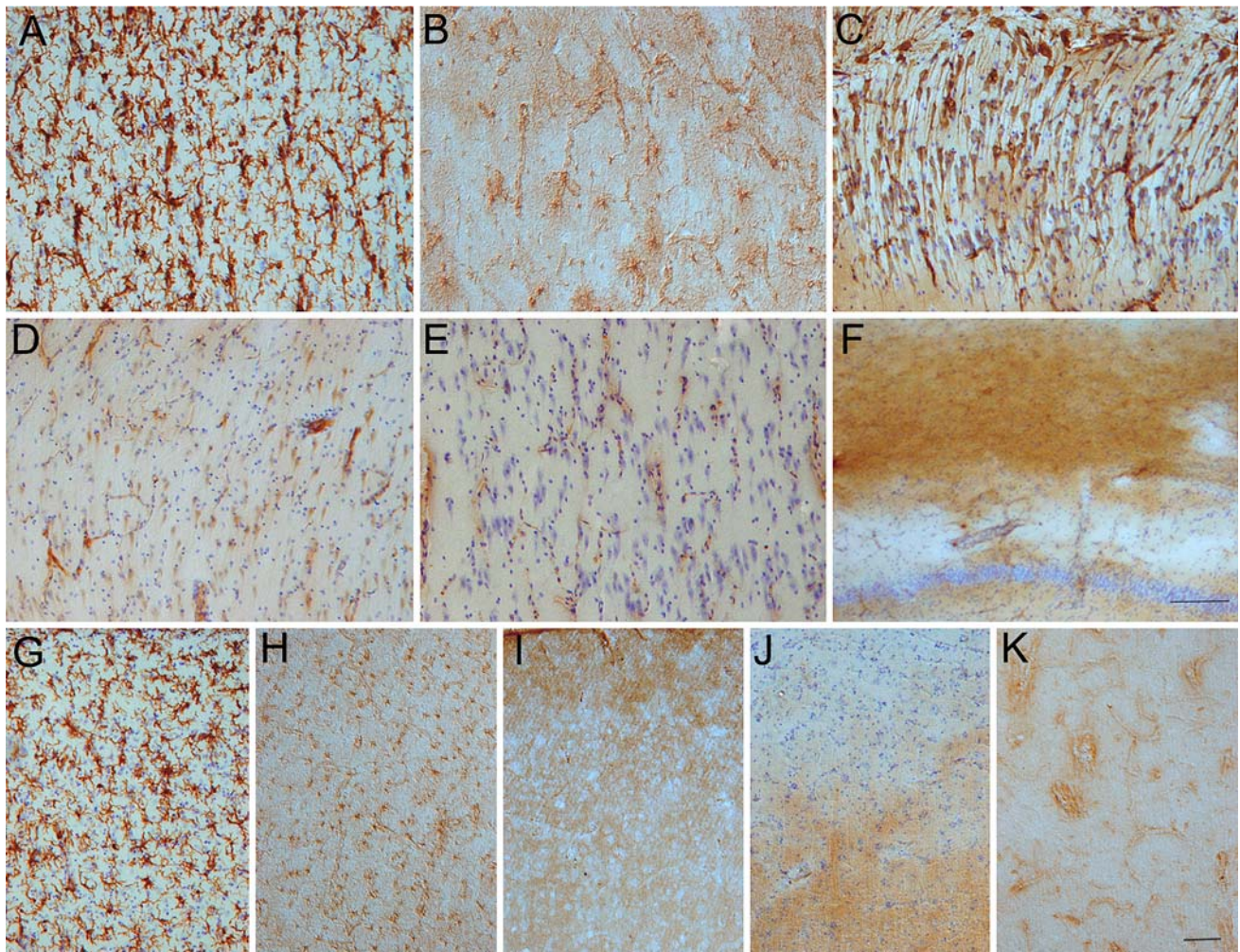


Fig. 4 Microglial activation, astrogliosis, and other markers of inflammation in area CA1 of the hippocampus. Extensive microglial activation (LN-3) (**a**) and astrogliosis (GFAP) (**b**) was observed along with an accumulation of C1q (**c**) and C4d (**d**) within neurons of the hippocampus. iNOS was also present at high levels in association with blood vessels (**e**). Within the white matter of the hippocampus, a dark diffuse cloud associated with the outer molecular layer of the dentate gyrus was positive for C4d (**f**). In

the frontal cortex, extensive microglial activation was observed in the case (**g**). The extent of astrogliosis was not as extensive as observed in the hippocampus (**h**). In contrast to the hippocampus, virtually no neuronal C1q labeling in the frontal cortex (**i**). As in the hippocampus, C4d was extensive in the white matter of the frontal cortex (**j**) and iNOS immunolabeling was associated with blood vessels (**k**). Sections counterstained with *cresyl violet*. Bar = 100 μ m

Discussion

In the current study we describe a patient with RP in whom the combination of dementia, visual hallucinations, and motor abnormalities suggested a diagnosis of DLB. Neuropathologically, however, he proved to have neither DLB nor AD. Instead there was severe nerve cell loss within the hippocampus, entorhinal cortex, and amygdala that was associated with patchy but widespread lymphocytic infiltration, predominantly within the leptomeninges. Further immunohistochemical studies revealed significant neuronal labeling with antibodies against C1q in the left hippocampus corresponding to areas of cell loss in the right hippocampus. Other markers of inflammation, used to identify acti-

vated microglia and other proteins involved in the complement pathway were all increased. Inflammation within the hippocampus and cerebral cortex could represent a neurobiological basis for the clinical signs of dementia, hallucinations, and a motor disorder.

There are few neuropathological studies of patients with RP and clinical signs of dementia in the literature. A profile of inflammation similar to our case was noted in a younger patient (52 years) who developed RP along with cognitive decline [45]. The patient died at the age of 57 years and microscopically the brain showed diffuse vasculitis affecting medium and small arteries and veins in at least 60% of the areas sampled. Some perivascular areas showed significant infiltration by lymphocytes into the parenchyma. “Burned out”

inflammatory lesions were noted in the frontal and temporal cortex. Significant necrotizing vasculitis and perivascular gliosis were noted in the medial thalamus and around the 4th ventricle. The hippocampus and in particular, the fascia dentata showed changes consistent with hypoxia, and there was inflammation in the fornix with scattered necrosis and vasculitis. The authors concluded that the patient had aseptic meningitis [45]. Hippocampal damage was common in both the current study and in this previous case and could account for the memory dysfunction observed in both patients.

In vivo imaging may be useful for detecting neurological inflammation due to RP and there are three previous case studies in addition to the current report describing MRI or CT studies. In one report, a 57-year old male with RP showed high intensity “spots” bilaterally in hippocampus and amygdala and the left paraventricular white matter, which progressed over time to involve also the caudate and putamen. This patient developed dementia with severe recent memory impairment, anxiety, and a mild depression [36]. A second case study reported multifocal gray and white matter high intensities in a 36-year old male with RP, and the authors suggested that it was related to cerebral arteritis [30]. A third 72 year old subject with a 20 year course of the disease and tremor revealed multiple spotted, confluent signal intensities consistent with cerebral angitis on MRI [11].

In our studies, multiple markers of neuroinflammation, microglial activation (HLA-DR), and activation of the complement pathways (C1q, C3b, C4d) were observed in the hippocampus. C4d labeling was also observed in frontal cortical neurons and in the white matter. In contrast, in the frontal cortex, C1q labeling was virtually absent. It is likely that the signs of neuroinflammation observed may have led to a dementia that resembled DLB. However, there are few studies examining neuroinflammation in DLB, with little consensus as to whether inflammation is a consistent feature of the disease [22, 27, 43, 48]. Complement proteins in the brain have been observed within Lewy bodies in DLB [22, 48] and in some [51] but not all studies [42] of Lewy bodies in Parkinson’s disease. The extent of microglial activation in the cortex of DLB cases is variably reported as being comparable to controls [43] or increased relative to controls [27, 28]. Inclusion of DLB cases with AD pathology can contribute to some of the variability in the observation of activated microglia [43]. However, cytokine production by activated microglial cells in the hippocampus of DLB cases is significantly higher than controls and may account for memory deficits observed in this form of

dementia [21]. Thus there is some evidence of overlap in the neuropathology observed in this study and in other reports of DLB with respect to inflammation, but more direct studies are necessary.

In the case presented here, RP is likely to be the cause of the meningoencephalitis, vasculitis, activation of the complement cascade, astrocytosis, and microglial proliferation, leading to severe hippocampal neuron loss that undoubtedly accounted for the patient’s dementia. A significant subset of patients with autoimmune diseases affecting connective tissue, including RP, also develop neurological disorders such as depression, dementia, psychosis, seizures, and tremors [33]. In RP the incidence of neurologic involvement is between 3 and 9.7% [52] with the most common features being headache, confusion, and altered levels of consciousness [4, 6, 17, 39, 45, 50]. Seizures, ischemic strokes, subarachnoid hemorrhage, dementia, cerebellar, and cranial nerve signs have all been observed in RP and may be associated with either cerebral vasculitis [33] or meningitis [4, 17, 26]. Moreover, CNS vasculitis may develop in the absence of detectable systemic vasculitis [33].

Molecular mechanisms of inflammation

The relative contributions of the adaptive and the innate immune systems to the neurodegeneration in the current case are difficult to determine because autoantibodies were not analyzed and measurements of T cell reactivity to previously described self-antigens such as collagen II and matrilin-1, were not performed. The fact that animal models of RP are only now becoming available has hampered the interpretation of the events that lead to secondary sites of inflammation that may lack the putative self-antigens that trigger the primary autoimmune event in cartilaginous tissues. However, two scenarios should be considered as likely possibilities for the CNS involvement in this case. The first involves expression of the protein antigens of the initial inflammatory response in RP, such as collagen or matrilin-1, in the cerebrovasculature. Presumably, the deposition of these antigens in the basement membrane of the leptomeninges and parenchymal cerebrovasculature provide sites for either autoantibody–antigen immune complexes to activate complement or T cell-mediated attack on vascular elements.

The second scenario is antigen-independent and requires only that activated T cells infiltrate into the CNS due to an innate inflammatory response in the brain. This may be triggered by peripheral inflammation, which is a likely possibility in RP [8, 25, 41, 47]. Alternatively, injury or infection in the cerebrovasculature or brain

parenchyma can activate innate immune responses, which can then be propagated in wave-like fashion to adjacent tissue also resulting in T cell infiltration [2, 20, 34, 35, 38]. Regardless of the specific inflammatory mechanisms involved in the activation of both the innate immune responses and the recruitment and activation of the T cells in the CNS in this case, management of the initial presentation of the RP might have prevented the onset of neuropathology and clinical dementia.

Several RP patients described in the literature with neurological signs responded well to immunosuppressive therapy. In one case, oral prednisolone (60 mg/day) treatment led to improved cognitive function (MMSE score increased from 23 to 29 out of 30) [36]. In a second case report, a 58-year old woman presenting with confusion and visual hallucinations, disorientation with respect to place and time, some motor facial weakness and gait ataxia in parallel with RP also responded well to dapson treatment [46]. Treatment with immunosuppressive agents may be used to reduce inflammation in tissues affected by relapsing polychondritis. However, the current patient's age (early 70s) and dementia argued against the aggressive use of steroids. In a recent report, two patients with RP and memory dysfunction and other signs of dementia responded to methylprednisone pulse therapy and showed significant improvement. However, memory difficulties could not be fully reversed. The findings in our case suggest that neuroinflammation led to neuron loss within the hippocampus, which would have resulted in lasting memory impairment [14]. The literature suggests that RP, if not aggressively treated, may be followed by inflammatory involvement of other tissues [33, 52].

There are several other neurodegenerative diseases or disorders involving the immune system that may mimic DLB clinically in a manner similar to that described in the current study. For example, parkinsonian symptoms and dementia can be observed in progressive supranuclear palsy [40], corticobasal degeneration [3] and other types of parkinsonism-plus syndromes [9]. Further, Creutzfeldt–Jakob (CJD) disease can also be associated with atypical parkinsonian features [29], and patients with familial CJD may exhibit both parkinsonism and hallucinations [15]. Autoimmune disorders (e.g., multiple sclerosis) [7] or inflammatory diseases may lead to a rapid and progressive dementia with movement abnormalities [5, 18, 44]. Thus, RP may be another potentially reversible autoimmune disease that is associated with DLB-like dementia.

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