Persistence of Immunopathological and Radiological Traits in Multiple Sclerosis

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**Background:** Multiple sclerosis (MS) is a heterogeneous autoimmune disease of the central nervous system. The identification of 4 different immunopathological subtypes of MS raises the question of whether these subtypes represent different patient subgroups that can be distinguished according to their leading mechanism of myelin destruction or whether this is a stage-dependent process in the development of lesions in a given patient.

**Objective:** To document intraindividual immunopathological and radiological homogeneity of 2 different lesions in a single patient with relapsing-remitting MS over time.

**Design:** Case report.

**Setting:** A neuropathological referral center for inflammatory demyelinating diseases of the central nervous system.

**Patient:** A 49-year-old woman with clinically definite relapsing-remitting MS.

**Main Outcome Measures:** Radiological and immunopathological analysis of MS lesions.

**Results:** Identical pathological findings in 2 different MS lesions separated by more than 2 years were identified. These lesions displayed similar and distinct radiological features on cranial imaging.

**Conclusions:** In this patient we were able to show the same antibody/complement-mediated lesion pathological findings with compatible identical ring enhancement on T1-weighted magnetic resonance images and hypointense rims on T2-weighted images after an interval of 26 months. Our observations support the concept of intraindividual homogeneity of a given immunopathological MS subtype.

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**MULTIPLE SCLEROSIS (MS)** is known for its clinical, radiological, genetic, and pathological heterogeneity. Pathological heterogeneity in MS is still a matter of debate, especially whether lesion heterogeneity within a given patient is a stage-dependent process, or whether patient subgroups can be distinguished according to their leading mechanism of myelin destruction. By identifying 4 different immunopathological subtypes of MS, the latter hypothesis favors homogeneity of lesion pathological type in a given patient, with interindividual heterogeneity among different patient subgroups. It is still unclear, however, whether these immunopathological patterns of MS lesions persist over time within an individual patient with MS. To help clarify this issue, we studied 2 consecutive brain biopsy specimens from a single patient with MS. Because multiple brain biopsy specimens from patients with proved inflammatory demyelinating disease are rare, little is yet known about pathological findings in individual lesions over time.

**REPORT OF A CASE**

A 49-year-old white woman with clinically definite relapsing-remitting MS according to the criteria of McDonald et al was operated on twice within 26 months for purposes of differential diagnosis, whereby 2 different brain lesions were sampled (differential diagnosis was high-grade glioma or brain abscess for the first biopsy and lymphoma for the second). Both tissue samples were analyzed by conventional histology as well as immunocytochemistry. The patient's history was evaluated retrospectively with respect to neuroradiological findings, disease course, and response to therapy.
During an observation period of 4.5 years, the patient experienced 3 clinical attacks of MS. The first attack coincided with a left frontal lesion, leading to lack of concentration, disturbance of memory, amnestic aphasia, and mild weakness in her right arm. A brain biopsy specimen showed inflammatory demyelination. The patient’s condition improved clinically without therapy, and she was discharged with the diagnosis of a clinically isolated syndrome, while the lesion resolved spontaneously as seen on follow-up cerebral magnetic resonance images (MRIs). Results of repeated analyses of the cerebrospinal fluid were always within normal limits; in particular, oligoclonal bands were absent. The second attack occurred 6 months later and caused acute vertigo, ataxia, and mild dysarthria due to a lesion within the right-sided cerebellar peduncle. Therapy with high-dose intravenous methylprednisolone (Urbason) resulted in partial recovery. Because the diagnostic criteria for MS according to McDonald et al were fulfilled, immunomodulatory therapy was suggested but refused by the patient.

A severe and sudden left-sided sensorimotor hemiparesis occurred 1 year later. Cerebral MRI demonstrated a new tumefactive lesion in the right-sided frontoparietal white matter. Symptoms were refractory to corticosteroids and treatment was changed to therapeutic plasma exchange. Although clinical signs improved significantly and lesion size diminished, the patient remained with residual symptoms. The patient refused a therapeutic approach with mitoxantrone hydrochloride. Instead, she consulted another hospital, where a biopsy was performed of the new large lesion seen on MRI to exclude lymphoma. Histopathological examination showed an acute inflammatory demyelinating process. Repeated high dosages of corticosteroids, as well as immunosuppressive therapy with cyclophosphamide, proved ineffective. Further aggravation of symptoms and lesion progression visible on MRIs led to another treatment effort with therapeutic plasma exchange followed by 2 intravenous applications of the monoclonal anti-CD20 antibody rituximab within 4 weeks. B cells were completely eradicated in peripheral blood as seen by fluorescent-activated cell sorter analysis. The patient’s condition finally stabilized, and the lesion decreased in size, resulting in a large hypointense T1 lesion on follow-up MRIs. No further relapses occurred.

In summary, the patient had 3 attacks since the appearance of her first clinical symptoms, based on 3 brain lesions at different locations. Thus, the criteria for dissemination of the disease in time and space were fulfilled and she was classified as having clinically definite MS with a relapsing-remitting disease course.

Of note, this patient belonged to a group of patients with MS demonstrating high anti-myelin oligodendrocyte glycoprotein (MOG) antibody titers. Serum IgG antibodies against native MOG markedly decreased months after application of a range of therapies mentioned herein. Meanwhile, the patient’s condition transitioned into secondary progressive MS, and she experienced slow clinical deterioration to an Expanded Disability Status Scale score of 4.5.

### RESULTS

Magnetic resonance imaging was used for diagnosis and monitoring of the disease. The first lesion was located within the white matter of the left frontal lobe. The gadolinium enhancement pattern was ring-shaped and displayed a hypointense rim structure on T2-weighted images colocalizing with the gadolinium ring. This lesion was subjected to biopsy by stereotactic guidance and resolved over time.

Six months later, a second small lesion in the right cerebellar peduncle appeared. This lesion completely enhanced with gadolinium and resolved over time. One year after this event, a large lesion developed within the right frontoparietal white matter. This lesion continuously increased in size over 7 months and showed ring-shaped gadolinium enhancement each of the 4 times it was studied during this period. Contrast enhancement again appeared ringlike and colocalized with a hypointense rim structure on T2-weighted images. This lesion was subjected to biopsy, and follow-up images showed persisting hypointensity in T1-weighted images in contrast to the first lesion in the contralateral hemisphere, which almost had completely resolved over time. Spinal MRIs showed no pathological changes. Since then, no further lesions were detected during follow-up; however, a mild symmetric atrophy was observed. Figure 1 shows a representative set of cerebral MRIs of the 2 lesions studied by biopsy.

### PATHOLOGICAL FINDINGS

Two brain biopsy specimens were investigated, the first from the left frontal white matter and the second 26 months later from the right frontal lobe. Both histopathological specimens showed early active inflammatory demyelination according to Bruck et al, as shown by myelin protein-positive degradation products in macrophages. Immunopathologically, both brain specimens displayed characteristics consistent with pattern II lesions (antibody/complement-mediated) according to Luccinetti et al, owing to the detection of the C9neo complement deposits in areas of active demyelination. Furthermore, both lesions displayed scattered T cells, large numbers of foamy macrophages (some of them coexpressing the acute activation marker MRP14), and a preserved axonal network. Interestingly, the second biopsy specimen showed a significantly greater loss of axonal structures in Bielschowsky silver impregnation than did the first biopsy specimen (24% vs 49% loss in relation to axon density in the normal white matter). No evidence of neoplastic cells or pathological changes other than inflammatory demyelination was found. Detailed pathological findings of the lesions are shown in Figure 2 and Figure 3.

### COMMENT

The present case of MS showed identical immunopathological features consistent with antibody/complement-
mediated demyelination in 2 brain biopsy specimens taken 26 months apart. Furthermore, MRI findings of these investigated lesions demonstrated distinct and identical features. Although the recurrent tumefactive lesions, the strong evidence of a peripheral antibody response, and the lack of cerebrospinal fluid oligoclonal bands are unusual, the correlation of tissue pathological findings with clinical and radiological findings as demonstrated herein

Figure 1. Cerebral magnetic resonance images of 2 inflammatory demyelinating lesions studied by biopsy. The first lesion developed in the left frontal area (A), and a second large lesion appeared in the right frontoparietal region 26 months later (B). Both lesions exhibit a ring-shaped gadolinium enhancement pattern on T1-weighted images (right), as well as colocalizing hypointense rims on T2-weighted images (left).
may provide important insights into lesion characteristics and, eventually, associated therapeutic implications.

Controversies exist regarding the heterogeneity of pathological characteristics of MS lesions. It is still unclear whether these observations may represent a stage-dependent lesional evolution or heterogeneity in pathogenic immune mechanisms that persist over time. Lucchinetti et al. recognized 4 different immunopathological patterns in active MS lesions according to their suggested leading mechanism of myelin destruction. Although patterns I and II are so-called autoimmune-mediated patterns, with (pattern II) or without (pattern...
I) additional complement deposits, patterns III and IV show marked oligodendroglial pathologic features. Although lesion pathological characteristics may vary among different patients with MS, these distinct patterns anticipate intraindividual homogeneity of a given immunopathological pattern. Conversely, Barnett and Prineas1 proposed that evidence of increased apoptotic oligodendrocyte cell death, absence of lymphocytes, or microglial activation as seen in pattern III probably represent early stages of new lesion formation, suggesting that pathological heterogeneity in MS is due to lesional evolution.

The patient described herein underwent repeated brain biopsies within a period of 26 months. Although the first biopsy specimen was obtained within 12 days after the first clinical presentation, the second biopsy specimen was taken from a lesion that had persisted for 7 months. Histopathologically, both lesions were in the earliest stages of demyelinating activity and exhibited identical pathological features consistent with pattern II pathological features. Even the first biopsy specimen, taken shortly after clinical presentation when the patient was not receiving any treatment, did not show any features consistent with so-called prephagocytic early lesion formation according to Barnett and Prineas,1 either in the demyelinating lesion itself or in the surrounding periplaque white matter.

Furthermore, MRI characteristics of the investigated lesions additionally support persistence of lesion pathological findings by showing identical MRI features with ring-shaped contrast enhancement on T1-weighted images and hypointense T2 rims. These MRI features were demonstrated as early as 6 days after disease onset and persisted over time until resolution. Ring-shaped contrast-enhancing MS lesions are found in a subset of patients with MS.9,10 In particular, pathological-radiological correlations attributed ring-shaped gadolinium enhancement and hypointense T2 rims to autoimmune-mediated pattern I and II lesions. These imaging features were absent in pattern III.4 Because the ring enhancement and the hypointense T2 rim may represent a structural phenomenon of active demyelinating lesions in patterns I and II, ie, macrophage accumulation at the lesion edge,11 imaging and pathological features may appear associated without necessarily having a pathophysiological link.

Apart from this, the patient showed marked T1 hypointensity within the second lesion studied on the follow-up images. Histopathologically, the second lesion showed a significantly greater axonal loss than the first,

Figure 3. Additional pathological findings in biopsy specimens of the earlier (A and C) and later (B and D) brain lesions. Immunocytochemical subtyping of the lymphocyte infiltrate shows a majority of CD3-positive T cells (A and B). A preserved axonal network (arrows point to single intact axons) was demonstrated by using immunocytochemical staining against SMI31 (C and D). However, signs of acute axonal injury are found in both lesions by labeling amyloid precursor protein–positive axonal spheroids (C and D, arrowheads in insets).
suggestions that the patient’s long-term impairment resulting from the last episode as well as her unresponsiveness to a number of therapies was due to the destructive nature of the second lesion.

Individual treatment regimens based on the immunopathological subtype seem promising. Selective response to therapeutic plasma exchange in corticosteroid-unresponsive patients with MS has already been described and is known to be associated with subtype II pathological features. Furthermore, treatment with anti-B-cell therapy was recently demonstrated to be highly effective in relapsing-remitting MS. In addition, high antibody titers to native MOG have been identified in a subgroup of patients with MS. The present patient belonged to this high anti-MOG antibody titer group. Ultimately, antibody titers against MOG dropped, suggesting that at least 1 of the medications given might have affected peripheral autoantibodies. However, the fact that this patient underwent several therapeutic interventions that may have interfered with one another does not allow us to unequivocally attribute the clinical response to a specific and selective therapeutic intervention. Another remarkable observation in this patient was that repeated analysis of the cerebrospinal fluid never showed pathological changes such as oligoclonal bands. Indeed, oligoclonal bands are found in most patients with MS, although few clinically indistinguishable subpopulations negative for oligoclonal bands have been described. To our knowledge, this is the first report documenting identical pathological and MRI features of 2 actively demyelinating brain lesions in a patient with relapsing-remitting multiple sclerosis during a period of more than 2 years. This case report supports the concept of intraventricular homogeneity of a given immunopathological MS pattern. Nevertheless, further extensive studies on a larger patient cohort will be needed to prove this hypothesis.

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