that inflammatory infiltration into the cortex through the meninges can also give rise to subpial cortical MS lesions in the early stages of the disease and in mild disease course. In conclusion, we present in vivo evidence for a lesion with cortical inflammation across a sulcus spreading from the meninges in early MS.

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In-vivo imaging of meningeal inflammation in multiple sclerosis: Presence of evidence or evidence of presence?

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Recent histopathology studies suggest the presence of meningeal inflammation in patients with multiple sclerosis (MS) that might be associated with subpial cortical demyelination and a rather worse disease course.[1] Although a radiologist is not a pathologist, diagnostic neuroradiology aims to visualize and to detect almost every (subtle) pathological feature of a disease to its full extent. To be able to translate histopathological results into radiological images will create an opportunity to visualize them in an in-vivo setting.

A good example of this in terms of MS pathology is the in-vivo detection of (subpial) cortical damage. It has been conclusively demonstrated that dedicated pulse sequences and the acquisition at higher magnetic field strengths can improve the detection rate of

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cortical lesions. This has led to a better understanding of important aspects and heterogeneity of in-vivo MS pathology and its impact on clinical outcome measures and disease progression.[2–5] However, with the available imaging techniques, we are still not able to visualize some of the smallest cortical lesions and the higher detection rate is to a certain degree counterbalanced by a disappointing inter-rater variability.[6]

In the same manner as the detection of cortical lesions, the detection of in-vivo leptomeningeal inflammation has become a hot topic in MS imaging studies. It feels like a déjà vu reading the overwhelming amount of literature. Once again, driven by indications from histopathological studies, magnetic resonance imaging (MRI) researchers try to prove the presence of a specific and potentially relevant aspect of MS pathology in the in-vivo setting. However, from the point of view of a clinical neuroradiologist, it remains questionable whether the actual presence of evidence on histopathology regarding meningeal inflammation, necessarily will lead to evidence of presence of such inflammation on in-vivo MRI.

It is quite intriguing that several reports claim that the use of contrast-enhanced three-dimensional (3D) T2-weighted FLAIR sequences at 3 Tesla (T) substantially improves the detection rate of lesions suggestive of such leptomeningeal inflammation, compared to conventional postcontrast T1-weighted images.[1,7,8] A recent report by Zivadinov and colleagues[9] in this journal additionally reported that what is currently thought to represent leptomeningeal contrast-enhancement on 3D FLAIR is associated with progression of cortical athrophy. Remarkably, the authors also present quite impressive data on the inter-rater variability in scoring leptomeningeal enhancement. A kappa value of 0.78, which is much higher than those reported for scoring cortical lesions,[6] warrants replication in future studies.

Another approach that is used to improve the sensitivity to the detection of leptomeningeal inflammation is the image acquisition at ultra-high field MRI operating at 7 T. In the current issue of this journal, Kolber and colleagues describe a cortical lesion affecting the postcentral and the adjacent precentral gyrus, thus labeling this lesion a "kissing lesion."[10] This lesion showed subpial enhancement after gadolinium administration at 3T MRI, which was acquired at the same day. The high-resolution 7T images that were acquired with a magnetization-prepared 2 rapid acquisition gradient echoes sequence (MP2RAGE) indeed show us a nicely delineated cortical type 1 lesion (mixed white matter and gray matter lesions) affecting both gyri.[8] With this, the case report shows important evidence that (active) type 1 cortical lesions can indeed appear in the early stages of MS, only after a disease duration of 2 years, with a mild disease course (EDSS = 0).

The authors furthermore describe that their 7T MP2RAGE images seem to show thickening of the leptomeninges in proximity of the lesion (Figure 1(k)–(l)). We must, however, place some doubt by these edematous meninges, and wonder if the hypointense rim-like border, which corresponds to the enhancing structure at the postcontrast 3T T1-weighted images, is not just part of the cortical lesion or the cortex itself. We have to keep in mind that so far, there has been no confirmation of the pathological substrate of this hypointense rim, which therefore warrants some caution in interpretation, as it was only shown on this relatively new sequence. In addition, we would expect that type 3 (subpial) cortical lesions will lead to meningeal inflammation (via complement deposition), rather than type 1 cortical lesions that are in fact white matter lesions not respecting the gray matter/white matter border and consequently invade the cortical gray matter.[11]

In literature, there is still doubt regarding the actual pathological substrate of subpial cortical lesions, regardless of their appearance on MRI. It remains unclear whether these may be induced by (a combination of) leptomeningeal inflammation, unrelated intra-cortical demyelination, or perhaps even by intracortical remyelination processes that do not reach the outer layers of the cortex. So, where recent publications such as this case report state to provide evidence of meningeal inflammation, we think we have to be cautious. Given the lack of histopathological verification data, it seems premature concluding that what these images show is in fact inflammatory infiltration through the meninges, and that this process underlies cortical pathology in the early stage of MS. However, with this caution kept in mind, we have to compliment the authors with their 7T MP2RAGE, which appears to be an interesting new sequence. We look forward to more studies on pathological specificity and evolution of cortical pathology in MS at 7T in vivo, preferably in combination with histopathological and animal model verification studies.

In conclusion, the in-vivo detection of leptomeningeal enhancement using MRI, with either contrast-enhanced 3D FLAIR at 3T or ultra-high field 7T MP2RAGE images, remains dangerous territory. How much we would like to be able to visualize and

to detect every (subtle) pathological feature of the disease MS, as clinical neuroradiologists and neuroscientists, we have to remain cautious in interpreting equivocal/debatable MRI phenomena as being definitive histopathological evidence of leptomeningeal inflammation in MS and its linkage to the development of (subpial) cortical lesions. More imaging data including histopathological verification is crucially needed in order to learn more about the MRI appearance of leptomeningeal inflammation and to exclude possible mimics of such imaging findings.

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