Fig S1

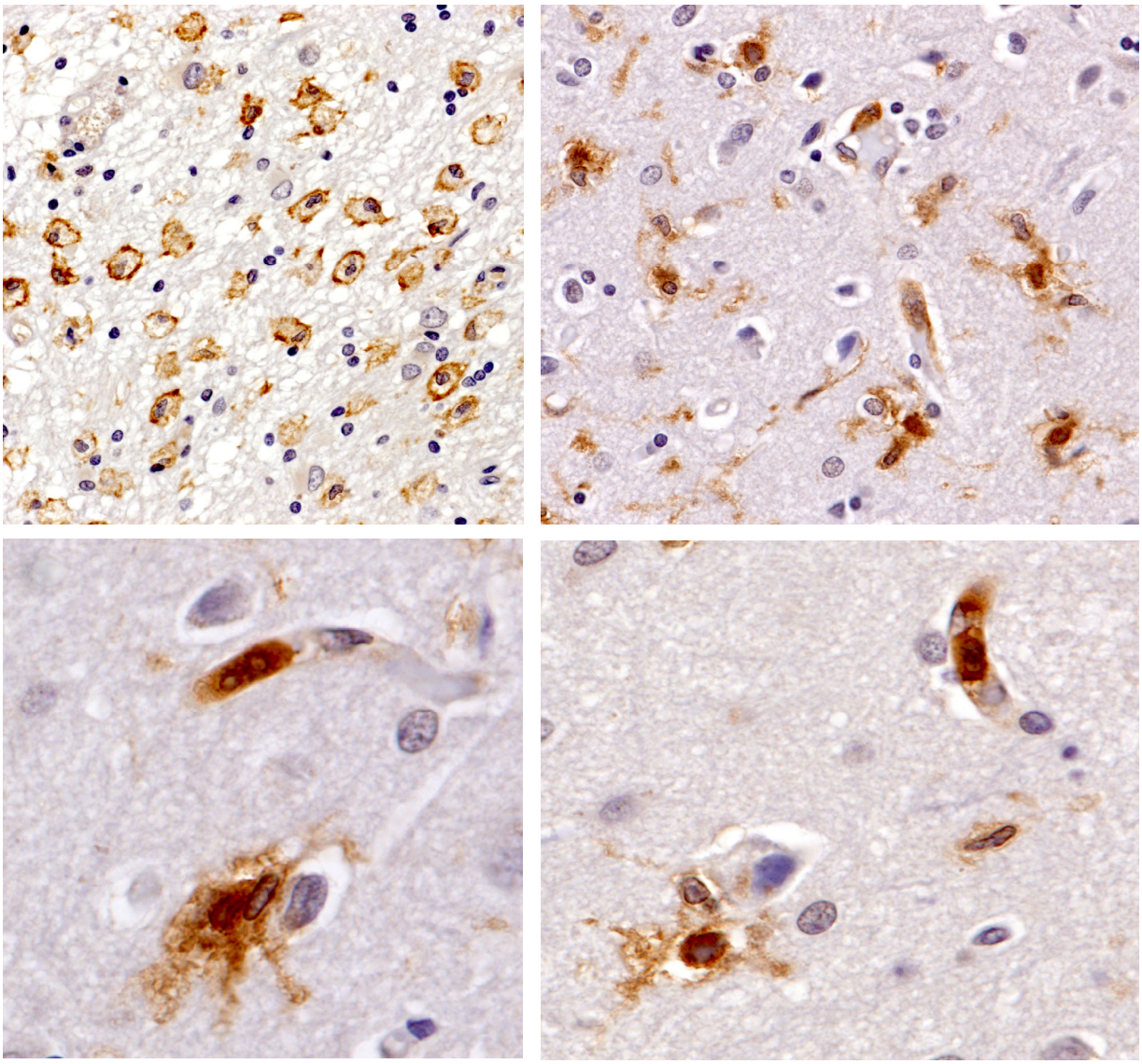


Fig S1 CD16+ monocytes and microglia: foamy macrophages (top left); nodules of ensheathed monocytes (top right); intravascular monocytes ('plugs') and reticulate microglia (bottom). (Case 16, CD16)

Fig S2

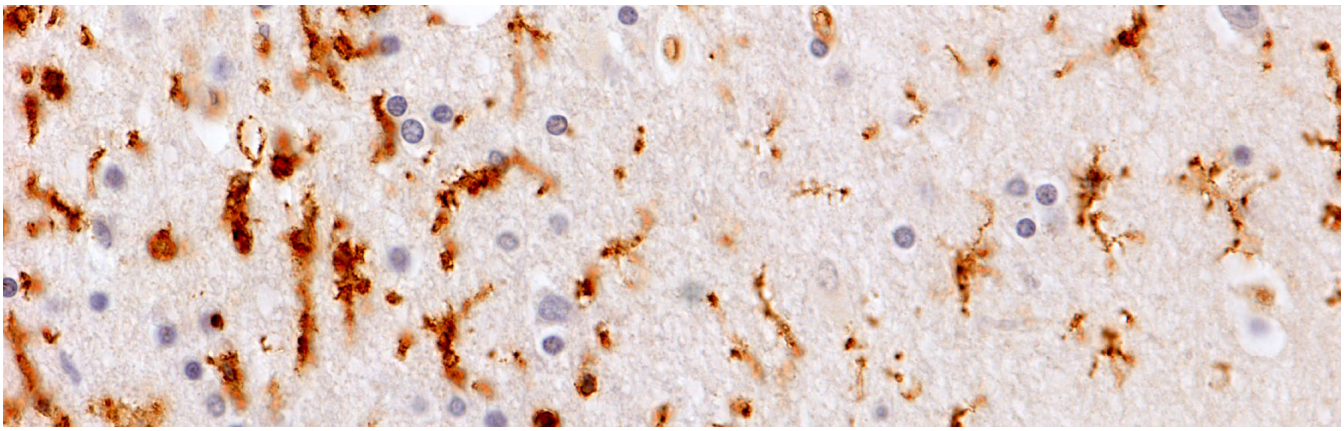
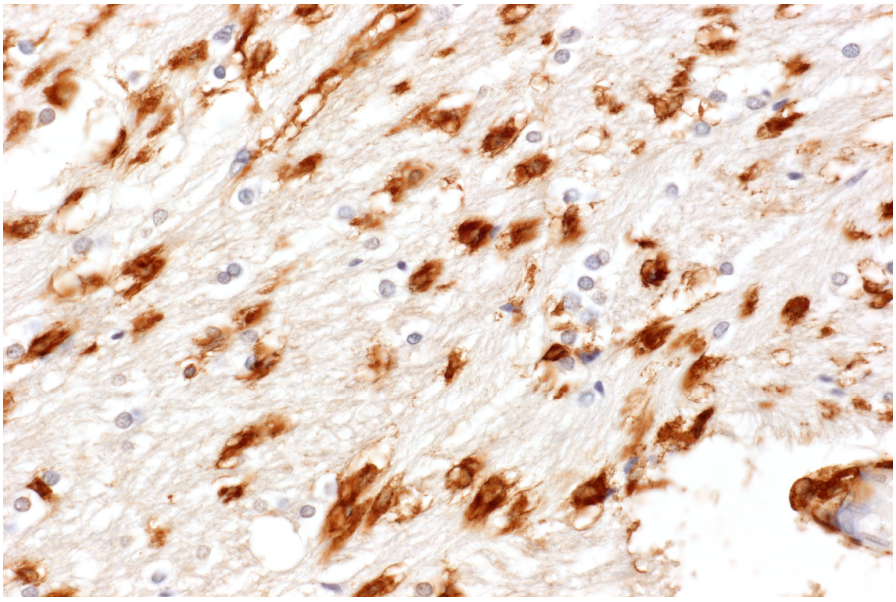
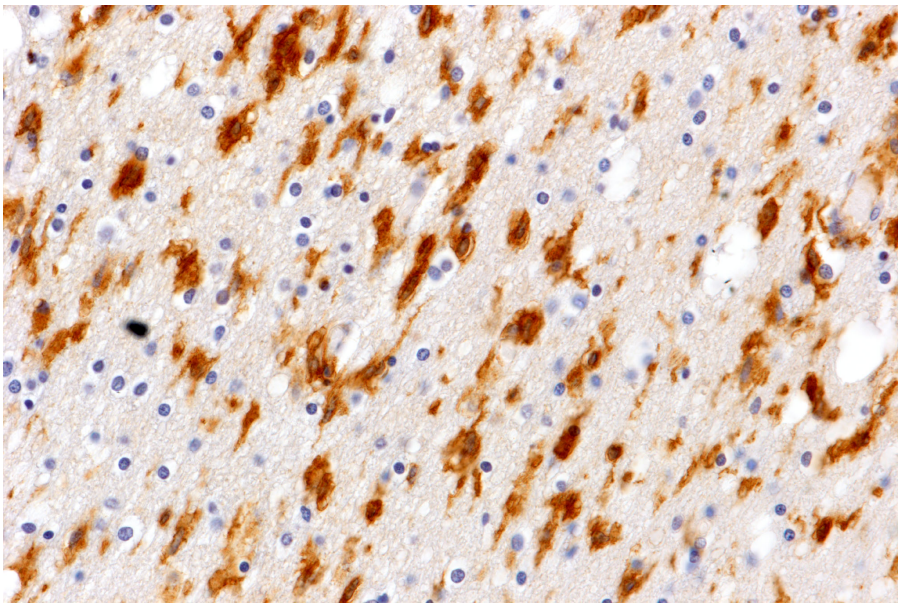


Fig S2 Non-ramified activated microglia (left of figure) as seen at one edge of plaque 4, Case 2. Ramified microglia (right of figure) are normal in appearance. (Case 2, plaque 4, CD45)

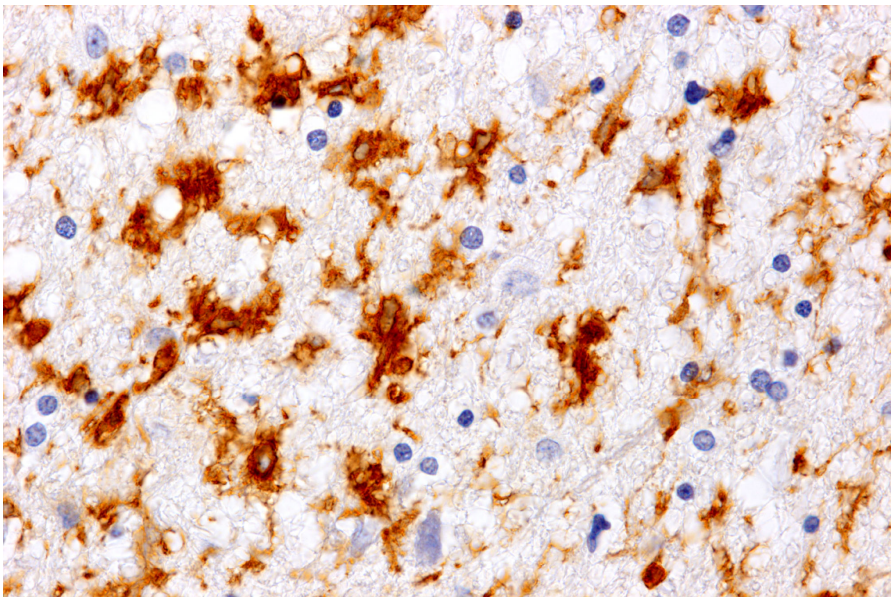
Fig S3



Activated MHCII+ microglia bordering intact white matter, Case 4.



Activated MHCII+ microglia bordering intact white matter, Case 16.



Activated MHCII+ microglia bordering intact white matter, Case 17.

Fig S4

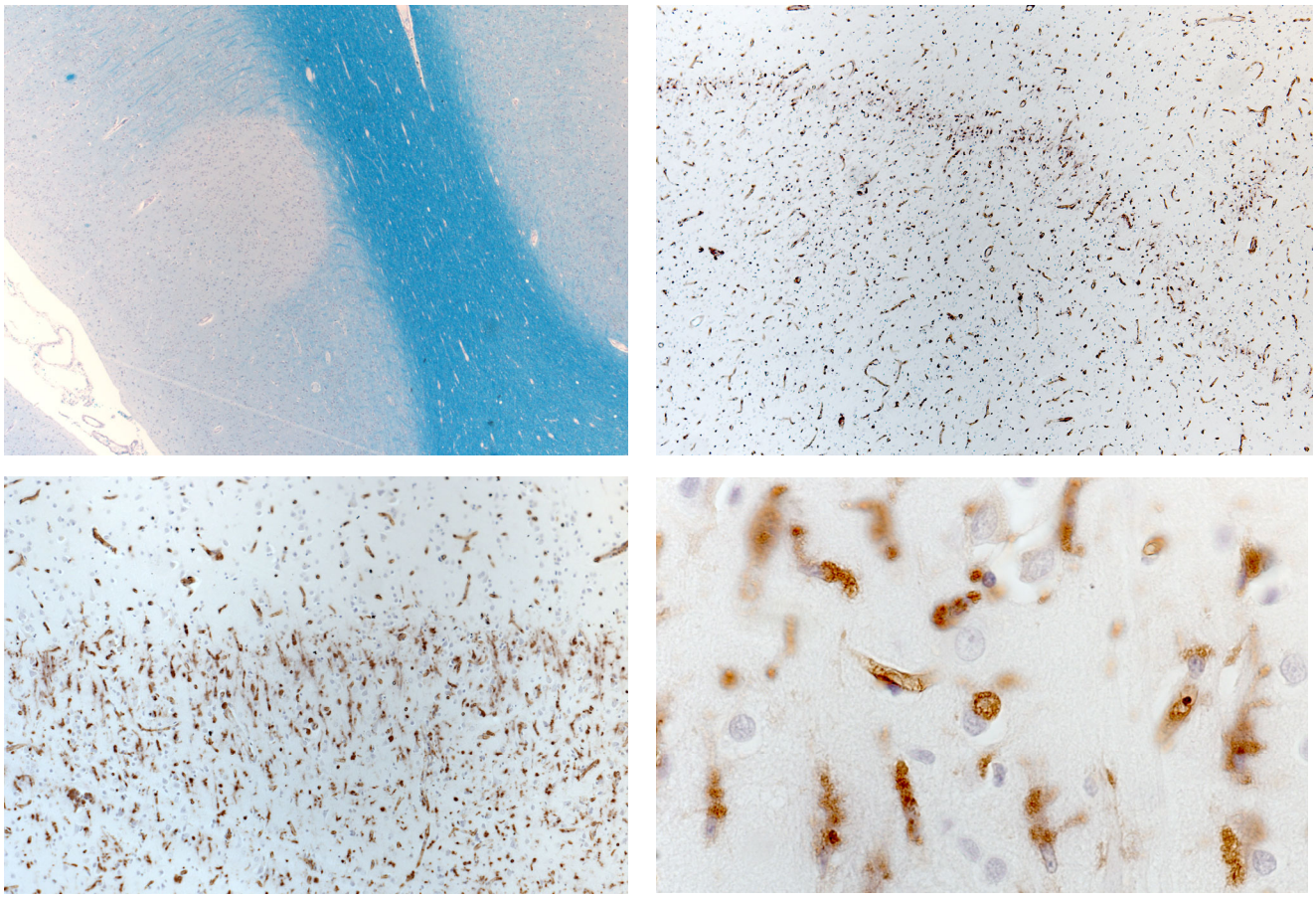
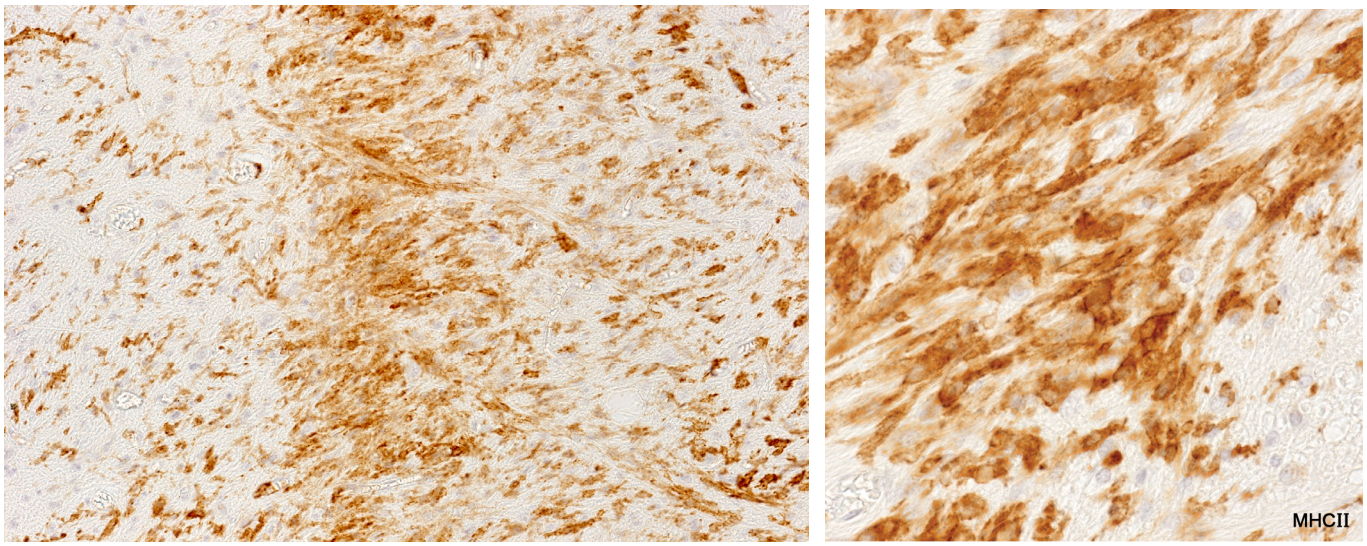
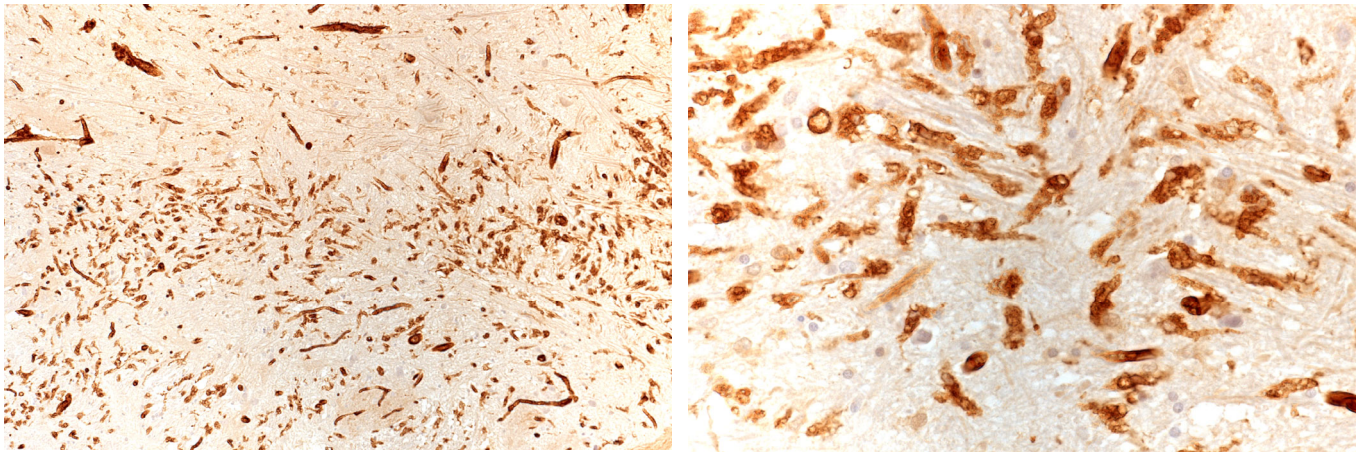


Fig S4 A narrow wall of RCA1+ microglia and capillaries outlines a typical small plaque located in the cerebral cortex. (Case 23, RCA1)

Fig S5



S5A MHCll+ wall microglia. (Case 24, plaque 3, MHCll)



S5B A wall of RCA1+ wall microglia and RCA1+ capillaries at the edge of a small brainstem plaque known to be immunoreactive for activated complement (C9neo). (Case 2, plaque 3, RCA1)

Fig S6

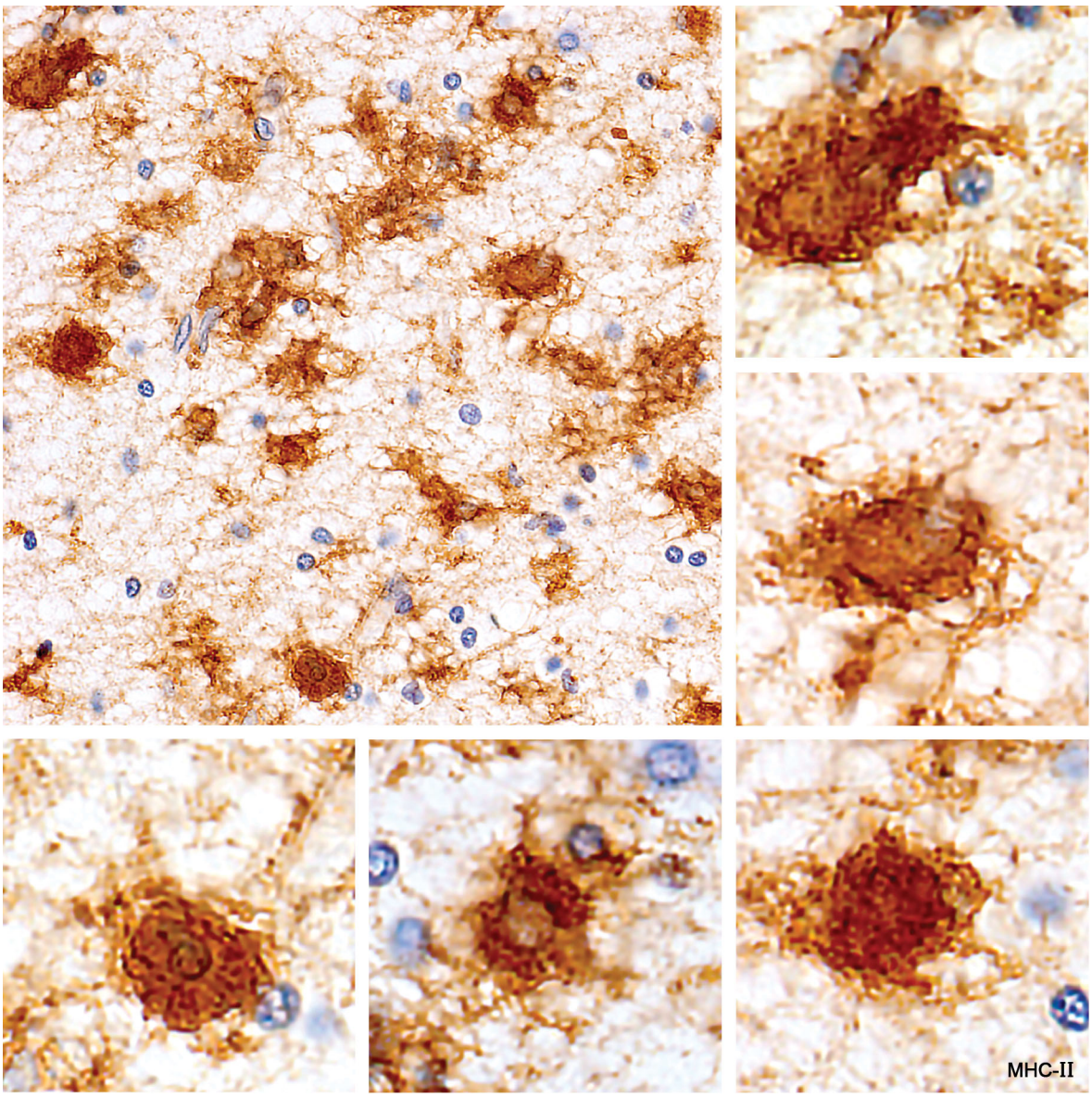


Fig S6 Nodules composed of compacted MHCII+ cells in intact white matter bordering an otherwise typical chronic plaque. (Case 16, MHCII)

Fig S7

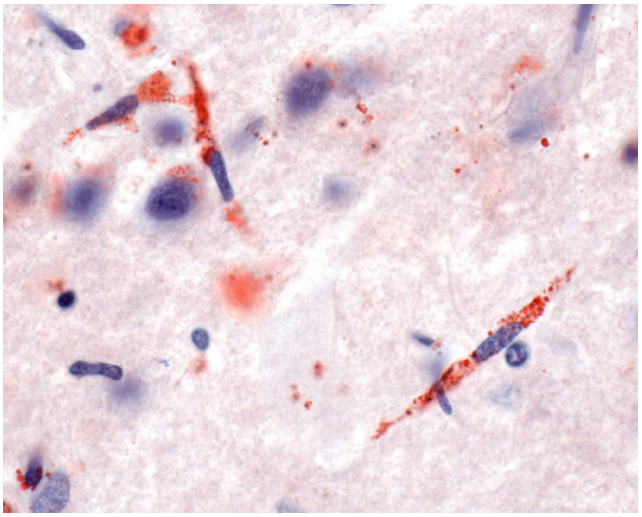


Fig S7 Spindle shaped phagocytes in a developing plaque in the cerebral cortex. (Oil Red O)

Fig S8

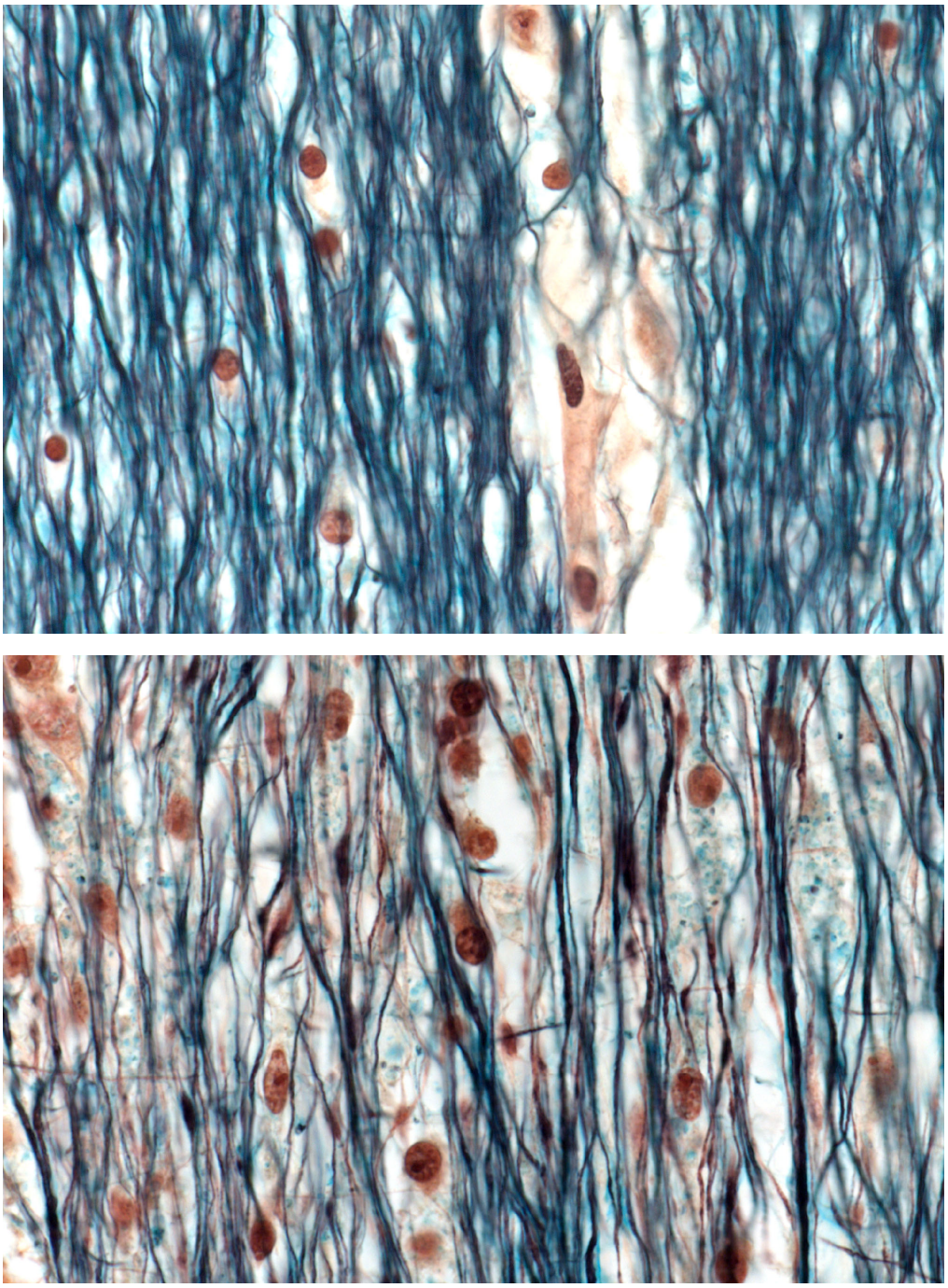


Fig S8 Round cells and phagocytes. **Top**: In a section stained for both myelin and axons, myelinated tissue bordering a developing plaque appears normally compact and with several (two) normal looking oligodendrocytes present. **Bottom**: The edge of the same plaque is less compact (more fluid-filled spaces), axons are intact, there is commencing loss of myelin, oligodendrocytes are hard to identify, and there are a number of large round cells, probably early phagocytes. (Case 5, **xxx)**

Fig S9

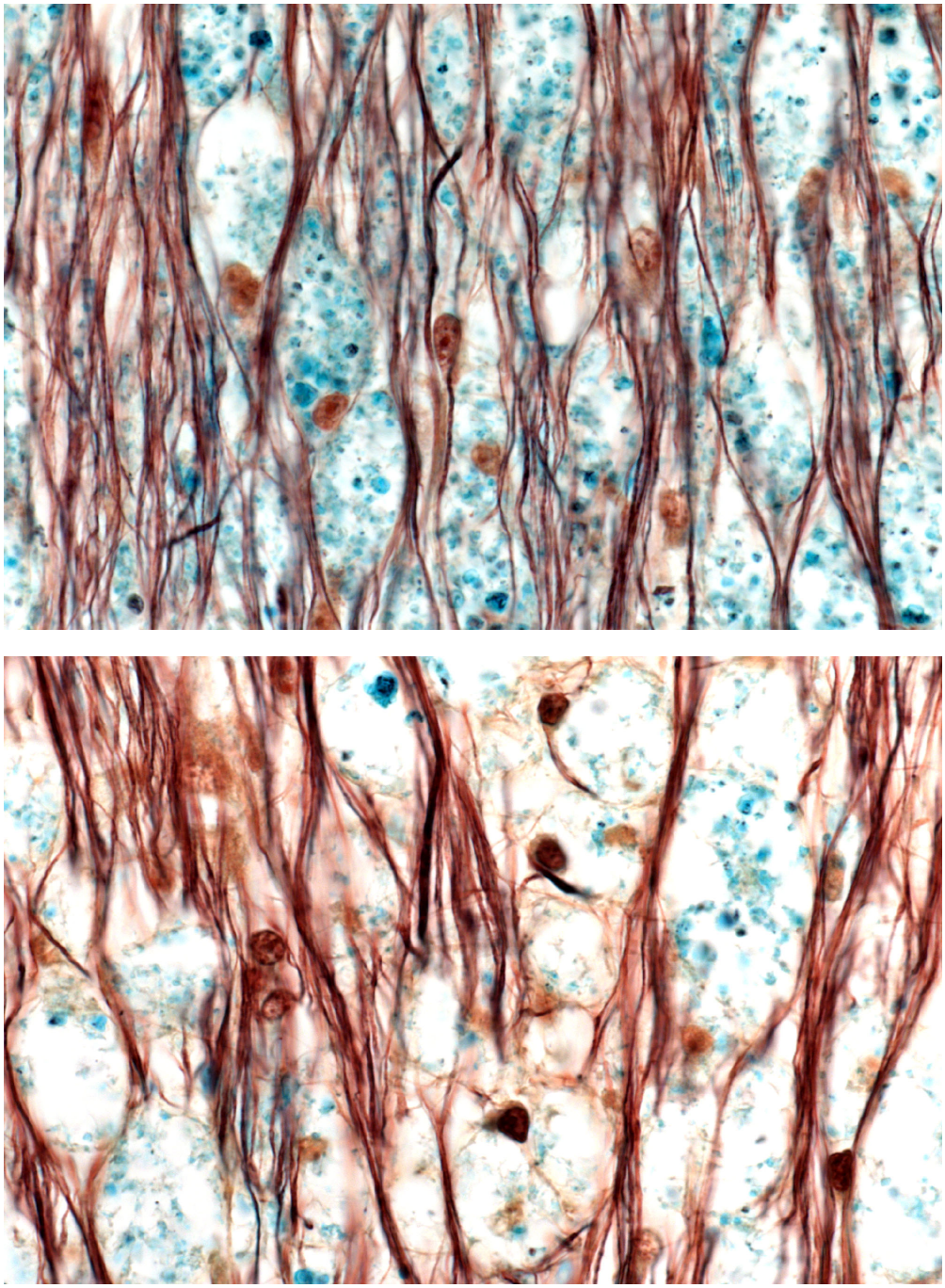


Fig S9 Round cells and phagocytes at the edge of the newly forming plaque shown in Fig S8. **Top**: Myelin loss is complete, phagocytes distended with particles of undigested myelin fill the extracellular space, and axons are preserved. There are no oligodendrocytes visible in this field. **Bottom:** Deeper in the lesion a field of foamy macrophages. (Case 5, **xxxx**)

Fig S10

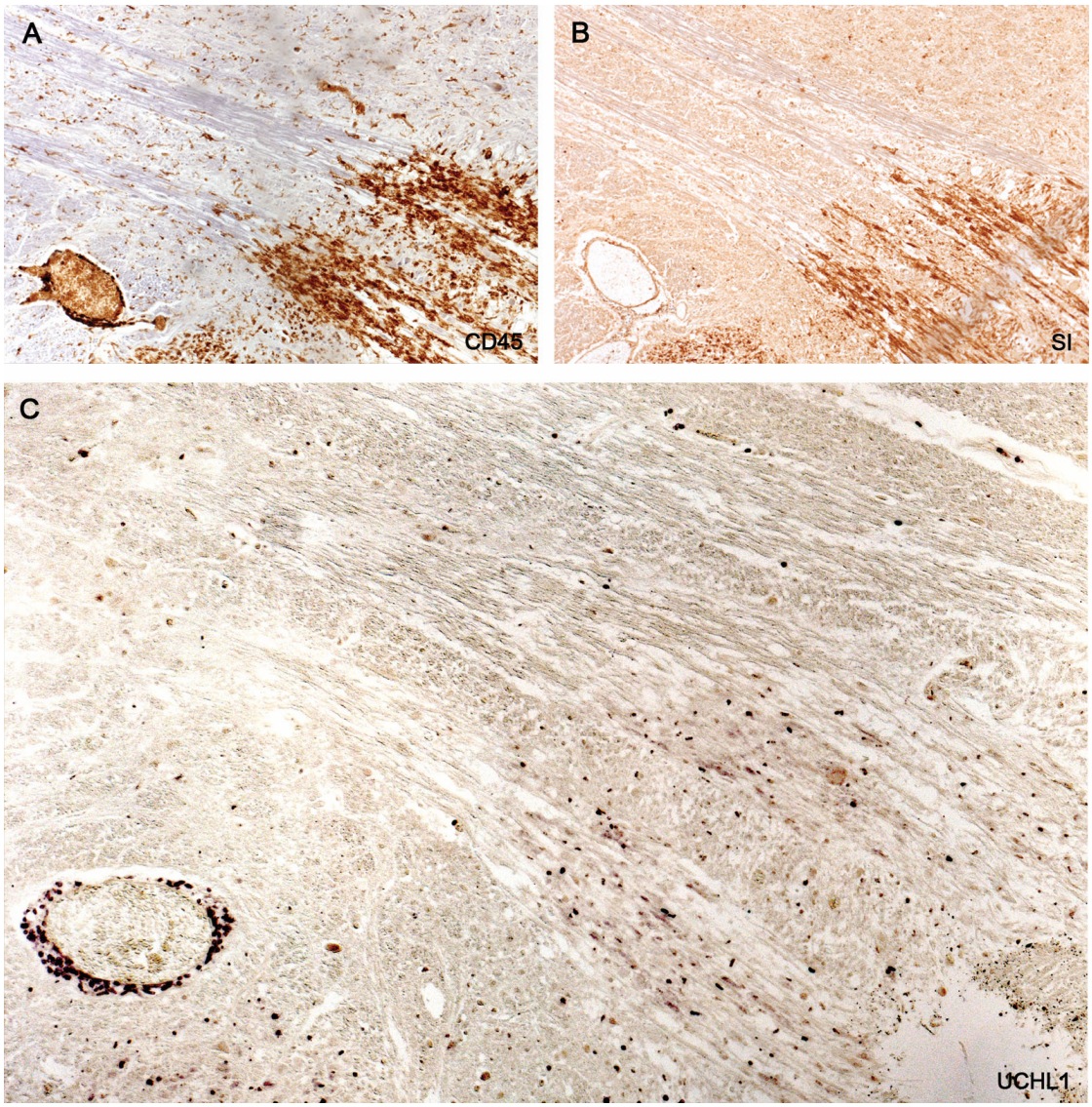


Fig S10 The expanding edge of a still- myelinated newly forming lesion (a plaque packed with wall microglia). **A**: CD45+ myelin phagocytes. **B**: myelin stains positively with biotinylated multiple sclerosis CSF IgG. **C**: UCHL1+ lymphocytes. (Case 2, plaque 1)

Fig S11

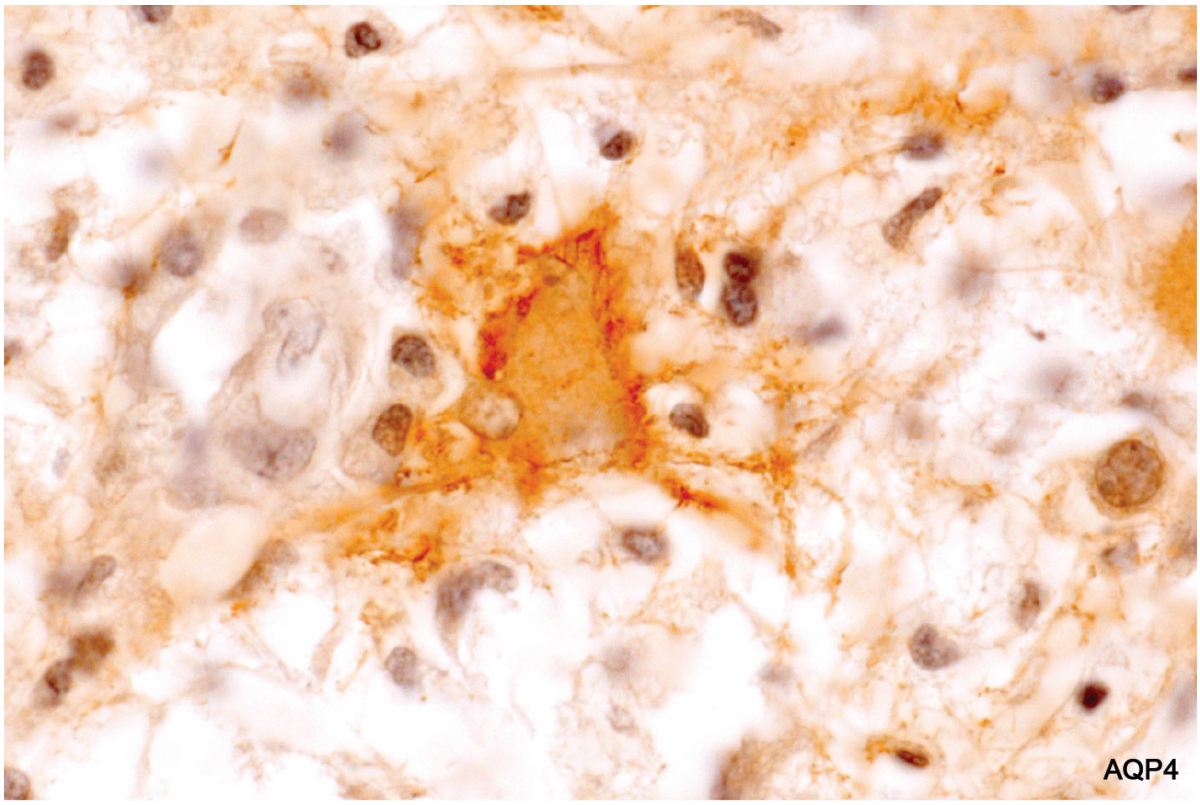


Fig S11 Destruction of an AQP4+ astrocyte by macrophages. (Case 14, AQP4)

Fig S12

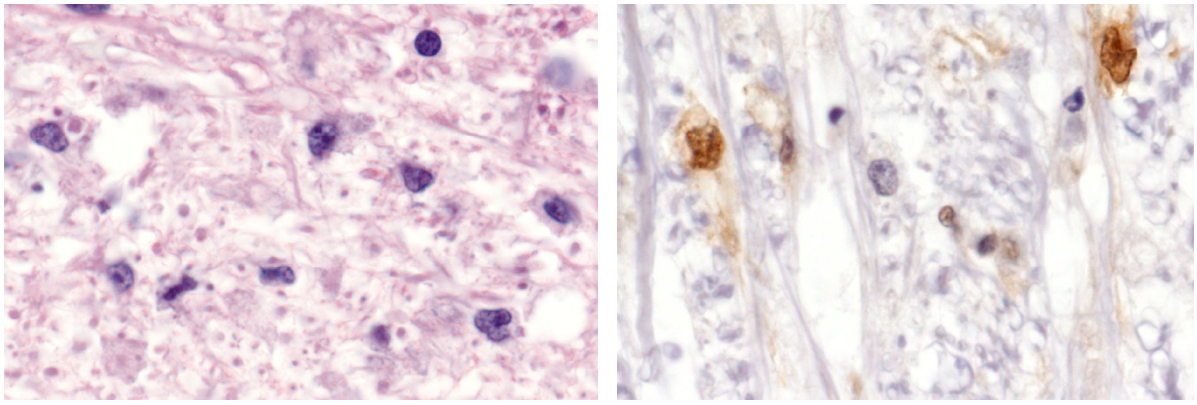


Fig S12 Infiltration and proliferation of early macrophages in normally myelinated white matter bordering a developing brain stem plaque. There are no normal oligodendrocytes present. Apoptotic oligodendrocytes in normally myelinated tissue were identified in other sections of the same lesion. (Case 9, Hematoxylin and E (left), proliferation cell marker PCNA (right))

Fig S13A

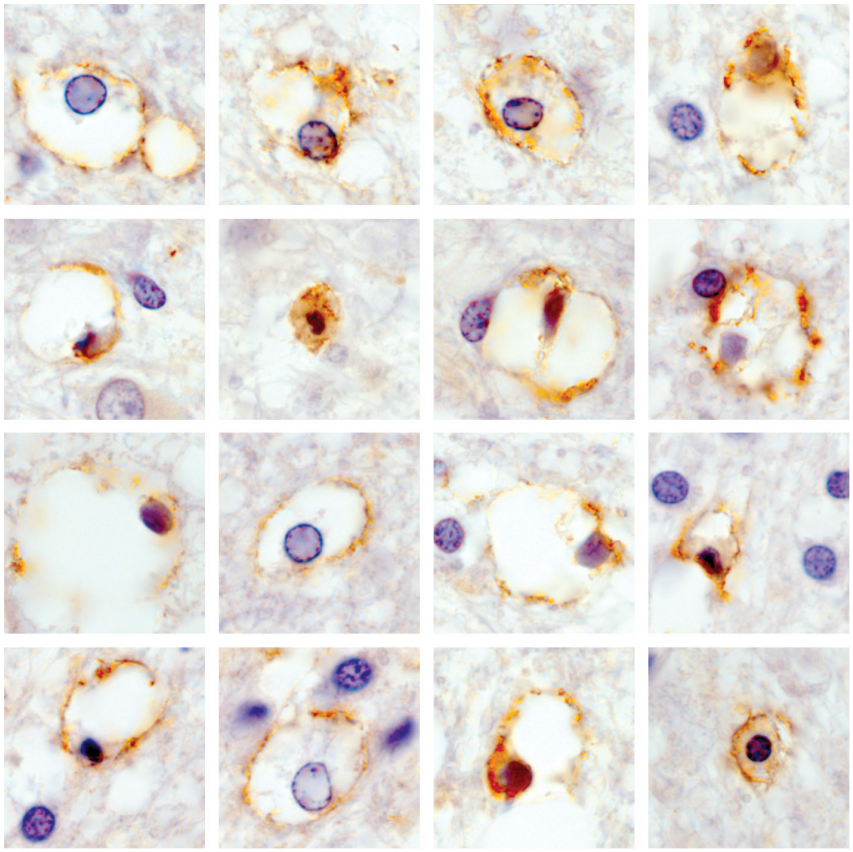


Fig S13A Degenerate oligodendrocytes immunoreactive for activated complement located in a partially remyelinated shadow plaque. (Plaque 4 Case 2, C9neo).

Fig S13B

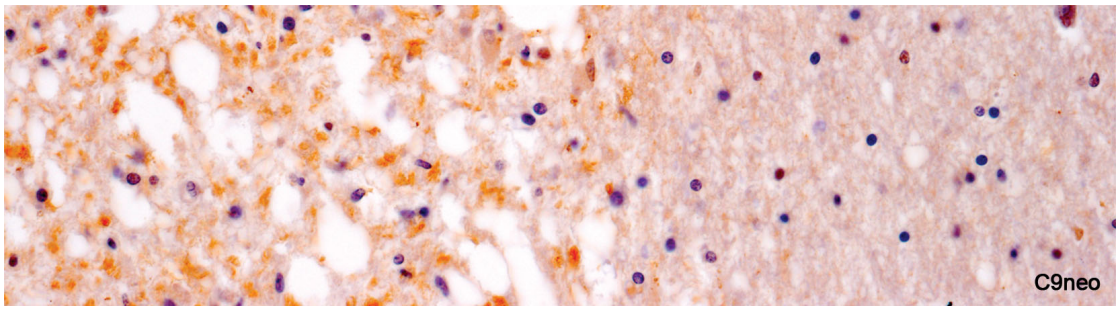


Fig S13B Perimeter of plaque 4, case 2, showing oligodendrocyte loss and complement - reactive vacuolated myelin. Parenchymal monocytes and MRP14+ phagocytes were largely absent in this partially remyelinated shadow plaque**.** (Case 2, C9neo)

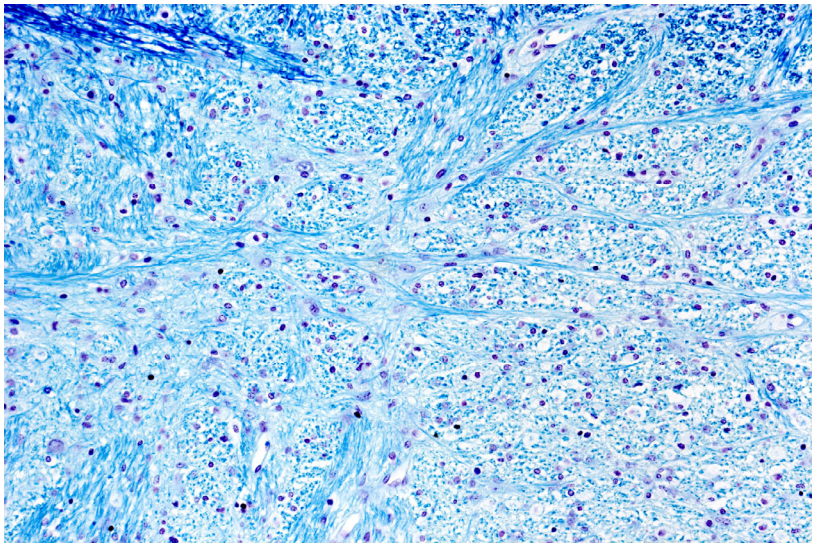


Fig S13C A remyelinated shadow plaque in a patient with early MS. A band of normally myelinated tissue can be seen at the top of the figure. (Non-index MS case, Luxol Fast Blue)

Fig S14

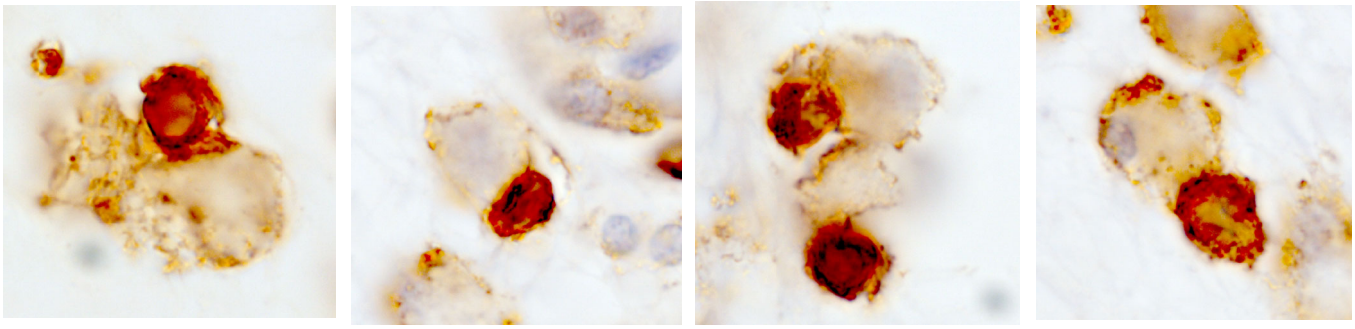


Fig S14A Monocyte /foamy macrophage contact. (Case 16, CD45)

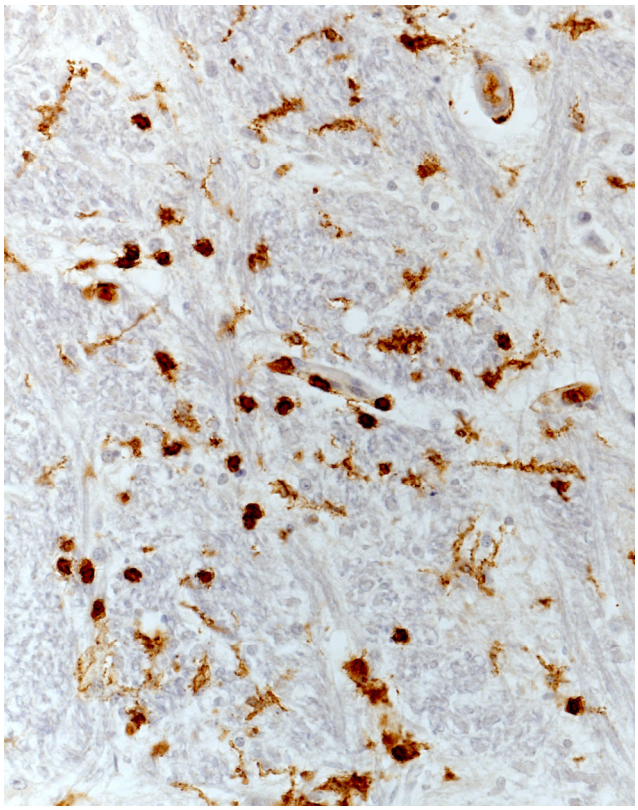


Fig S14C Perivascular monocytes, normal white matter. (Case 2, CD45)

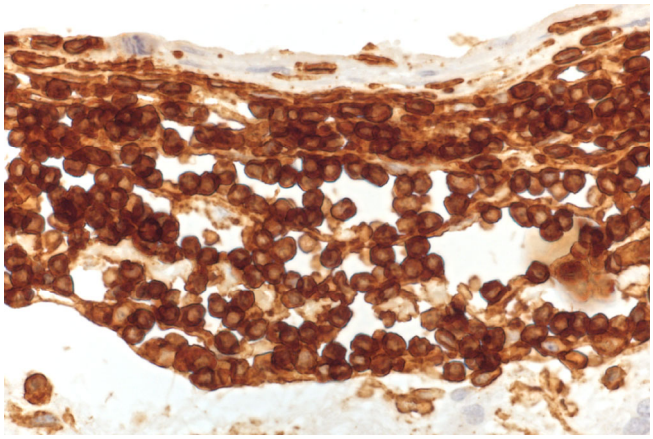


Fig S14B Perivascular space monocytes located in demyelinated tissue. (Case 3, CD45)

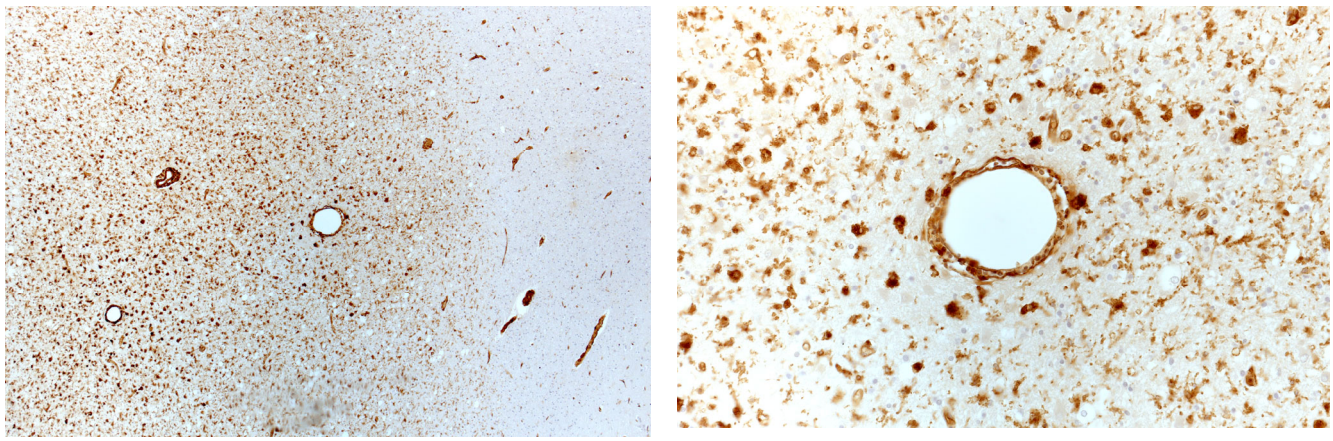


Fig S14D Parenchymal monocytes located around a blood vessel situated in a field of RCA1+ microglia. (Case 2 plaque 4, RCA1)

Fig S15

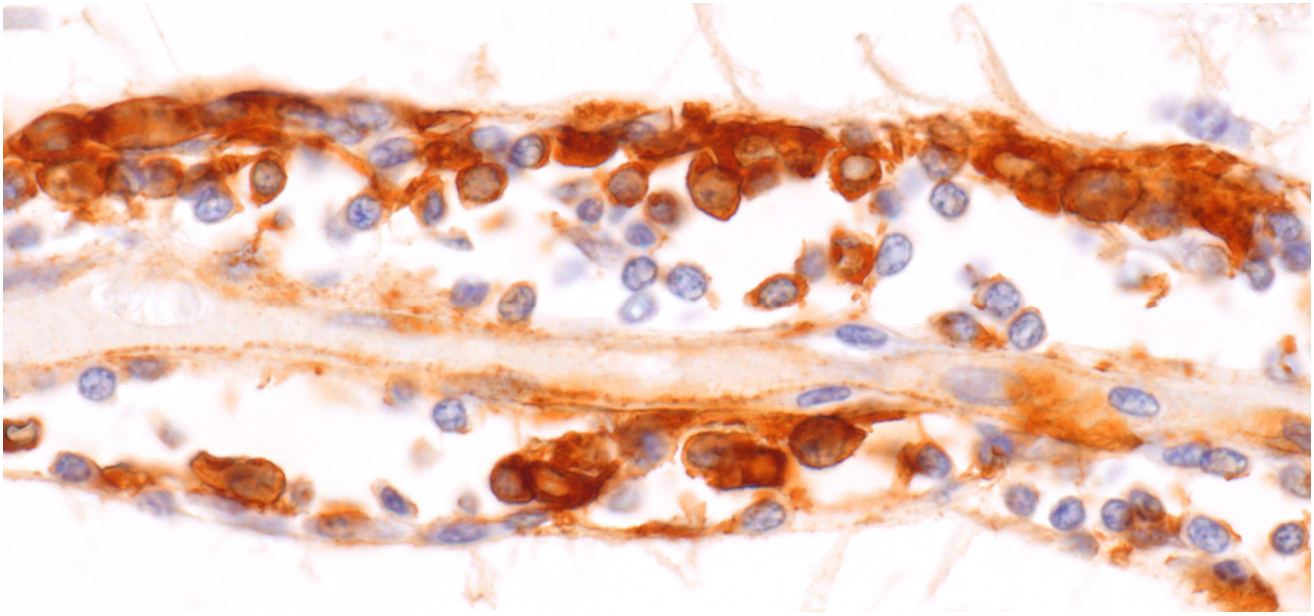
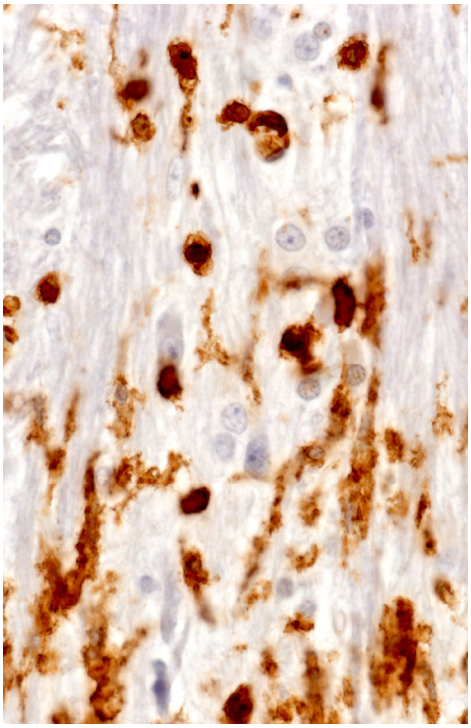


Fig S15A A perivascular cuff of MHCll-negative lymphocytes, MHCll-positive lymphocytes and MHCll-positive larger cells. The vessel was located in demyelinated tissue in a newly forming basal ganglia plaque. (Case 4, MHCll)



S15C Infiltrating monocytes and early phagocytes at the edge of an expanding exceptionally early newly forming plaque. (Case 2, plaque 1,CD45)

Fig S15B

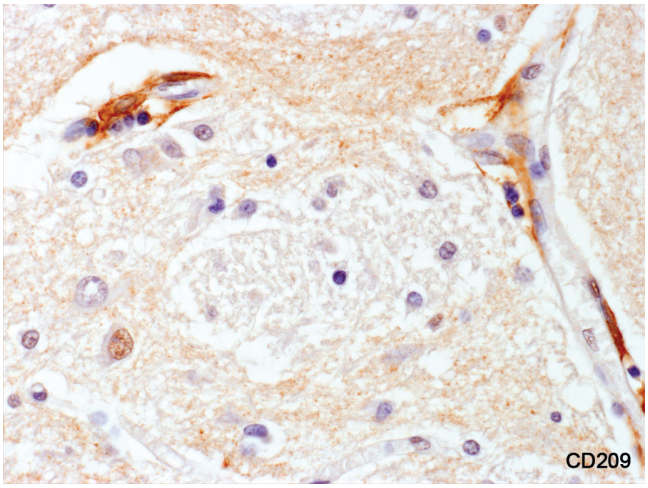


Fig S15B CD209+ dendritic cells in walls of small blood vessels in myelinated tissue bordering an expanding plaque. (Case 4, CD209)

Fig S16

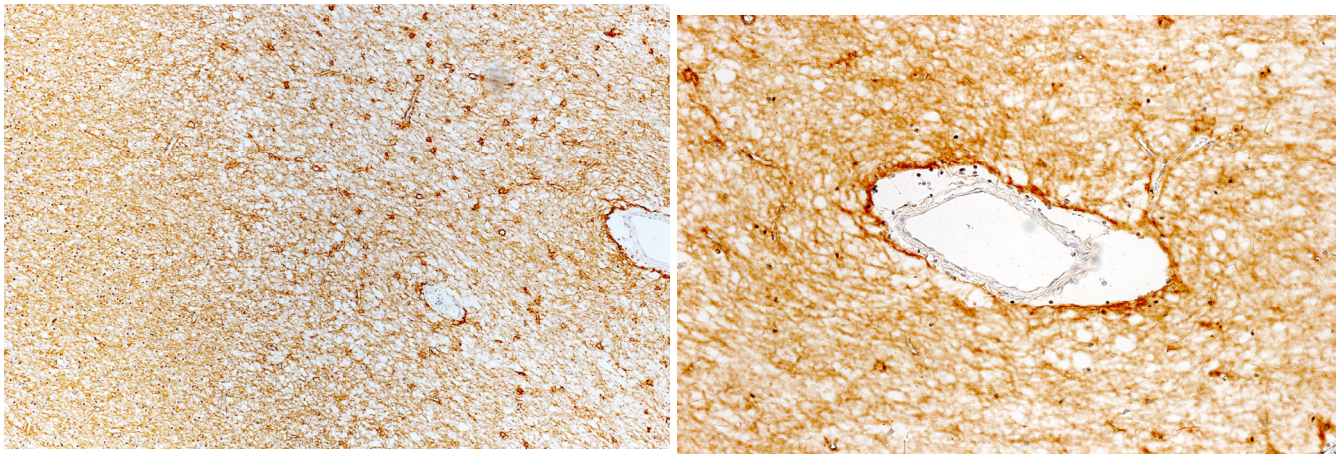


Fig S16A Chronic multiple sclerosis. Regenerated AQP4– positive astrocyte foot processes. (Case 16, AQP4)

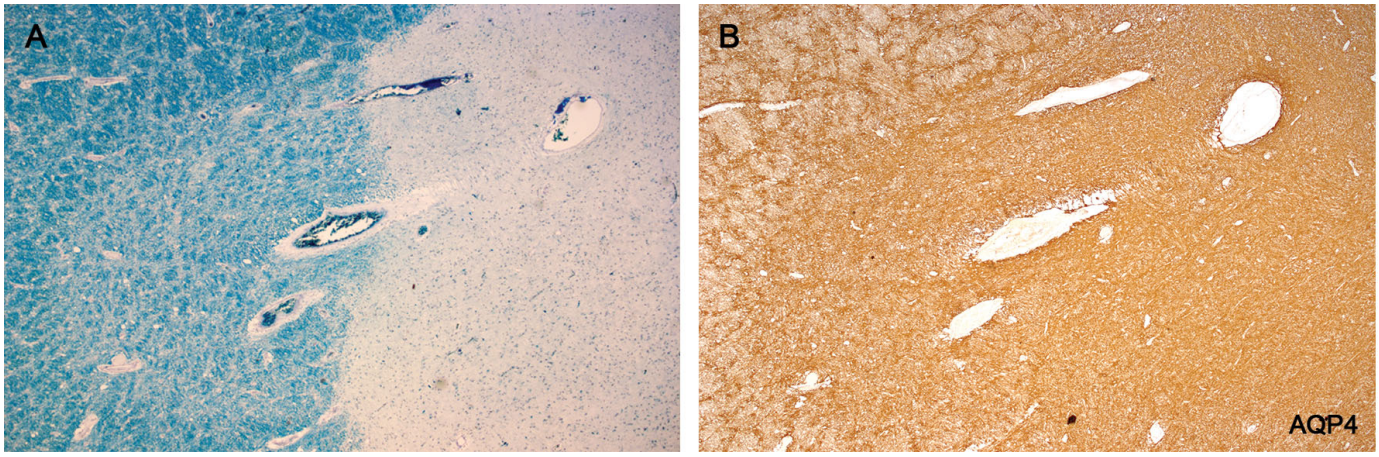


Fig S16B AB Chronic multiple sclerosis. Regenerated AQP4-positive astrocytes in a partially demyelinated shadow plaque. (Case 22, AQP4)

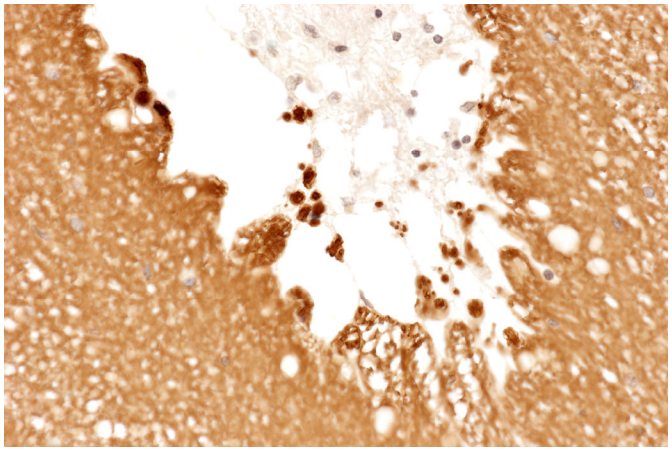


Fig S16C Chronic multiple sclerosis. Abnormally regenerated AQP4-positive perivascular glial limiting membrane astrocyte foot processes. (Case 22, AQP4)

Fig S17

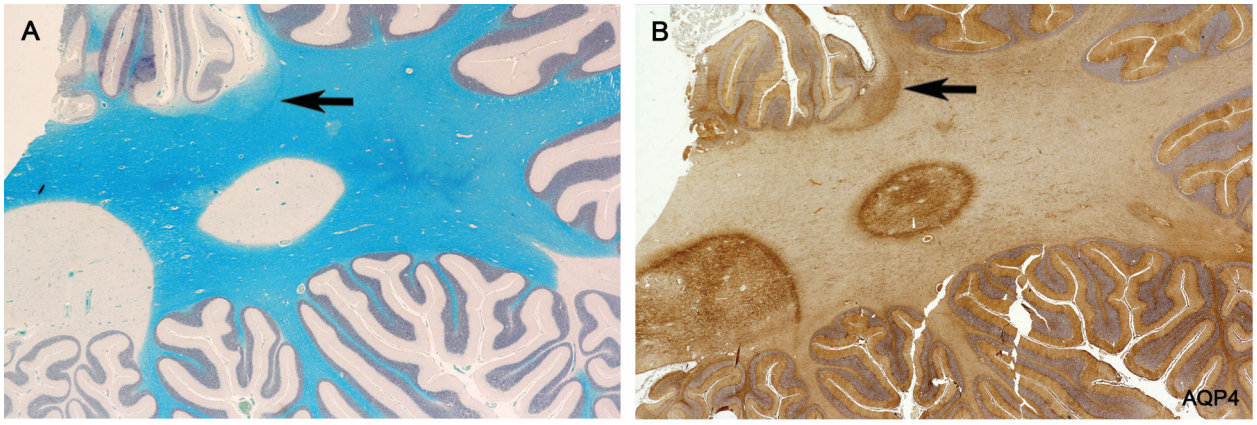


Fig S17 A magnified view of four plaques of different histological age in a patient with longstanding MS. **Top:** An old remyelinated shadow plaque (arrows). **Left**: A gliosed plaque filled with AQP4+ astrocytes and foamy macrophages. No LFB+ macrophages. **Center:** A gliosed plaque with numerous AQP4+ astrocytes, scant foamy macrophages , no LFB+ macrophages. **Right:** An old plaque, no foamy macrophages, fewer AQP4+ astrocytes. Edge walls of wall microglia, astrocytes and monocytes outlined two of the plaques, the one on the left and the one in the middle. (Case 18, left - Luxol Fast Blue, right - AQP4)

Fig S18

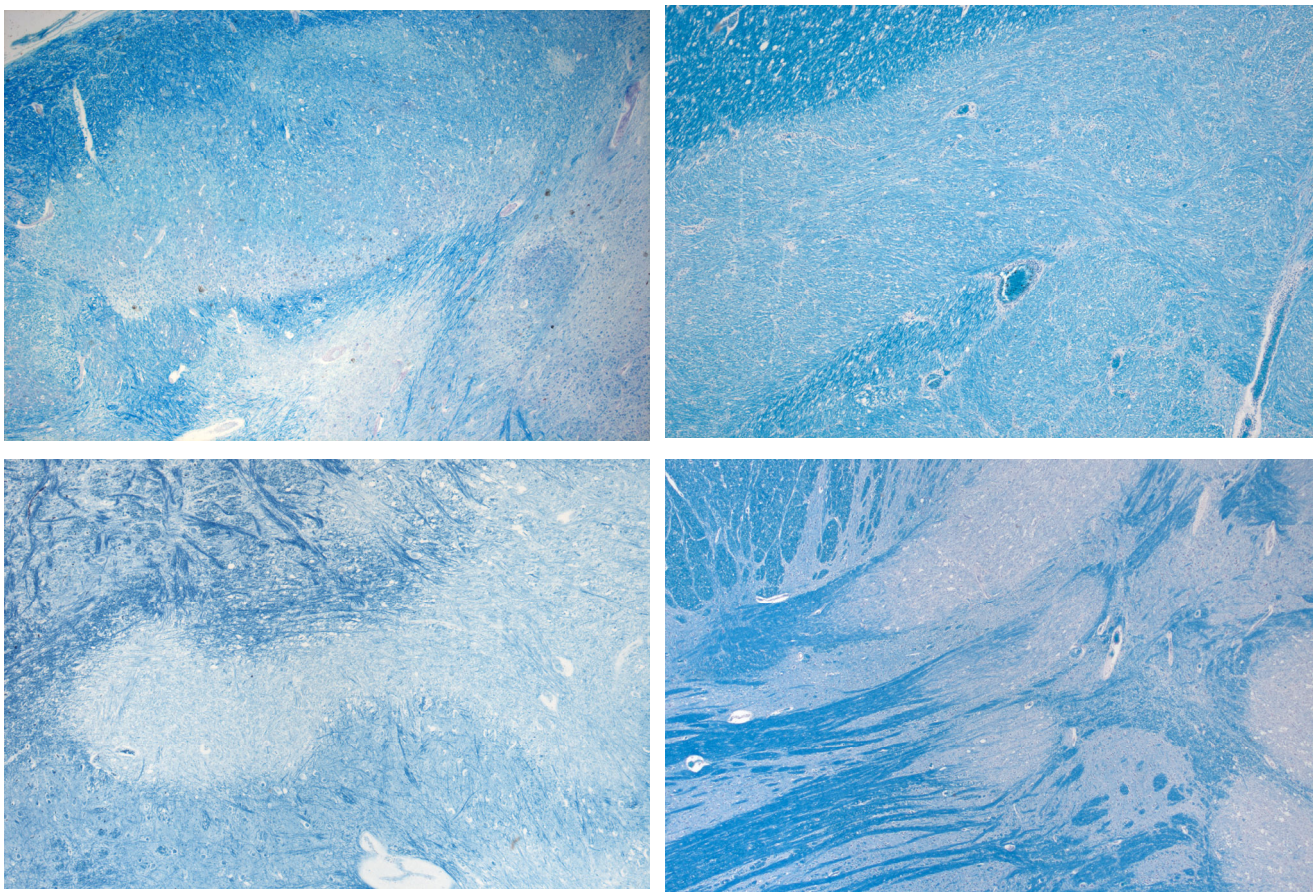


Fig S18A Four typical still-myelinated prephagocytic newly forming plaques. (Luxol Fast Blue).

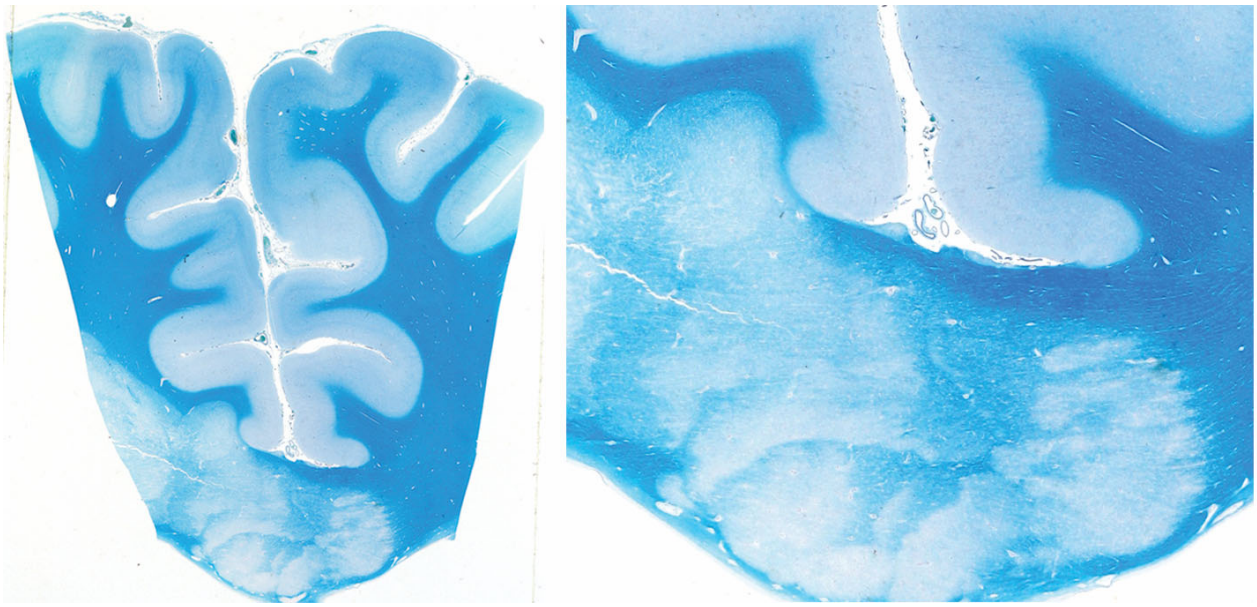


Fig S18B A still-myelinated prephagocytic plaque with very early commencing myelin breakdown. LFB+ macrophages were present but difficult to identify. The only phagocytes readily identifiable were intensely stained HAM56+ phagocytes present in small numbers scattered throughout the plaque. (Case 2, plaque 6, Luxol Fast Blue)