Imaging the Complications of MS Therapies

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Disclosures

- Almost all of my work is funded by the NINDS Intramural Research Program.
- Trainees in my lab have received support from the National MS Society, the American Brain Foundation, the Foundation of the Consortium of MS Centers, and the Conrad N. Hilton Foundation.
- We have Cooperative Research and Development Agreements with the Myelin Repair Foundation and Vertex Pharmaceuticals.

Not My Objective

- To give a comprehensive overview of the complications of MS therapy.

Main topics

- PML
- rebound
- herpesviruses

- *other interesting reports*

http://dx.doi.org/10.3174/ajnr.A5148

Current and Emerging Therapies in Multiple Sclerosis: Implications for the Radiologist, Part 1—Mechanisms, Efficacy, and Safety

Current and Emerging Therapies in Multiple Sclerosis: Implications for the Radiologist, Part 2—Surveillance for Treatment Complications and Disease Progression

C. McNamara, G. Sugrue, B. Murray, and P.J. MacMahon

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REVIEW ARTICLE

Multiple sclerosis update: use of MRI for early diagnosis, disease monitoring and assessment of treatment related complications

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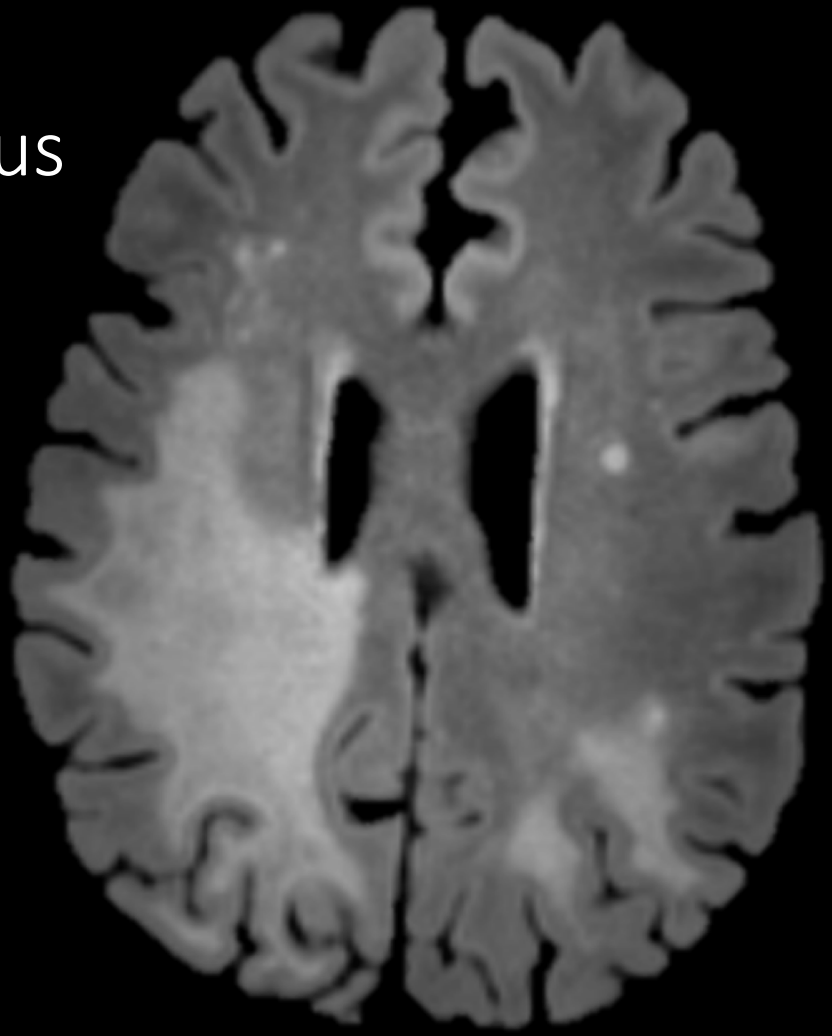
Progressive Multifocal Leukoencephalopathy (PML)

- Devastating brain infection caused by JC virus
- Immunosuppression (now commonly iatrogenic) is the primary risk factor
- ~25% mortality in the setting of MS
- Best treatment: immune reconstitution



Major risk factors for PML in MS

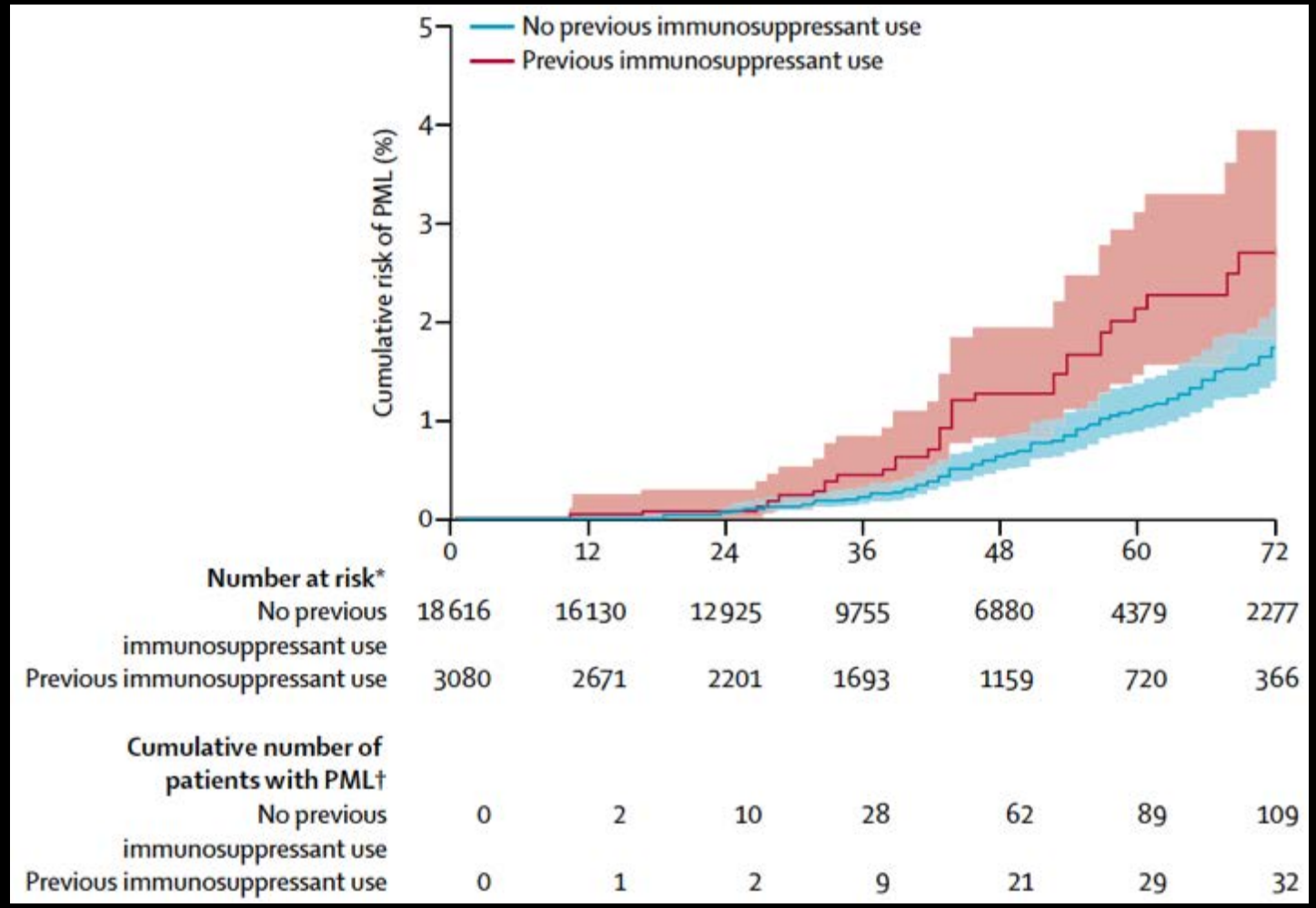
- immunosuppression for > 2 years
  - especially natalizumab
  - also reported: fingolimod, dimethyl fumarate, rituximab
- + serology for JCV (high JCV antibody index)
- prior immunosuppressive therapy raises risk

Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies

Pei-Ran Ho, Harold Koendgen*, Nolan Campbell, Bill Haddock, Sandra Richman, Ih Chang*

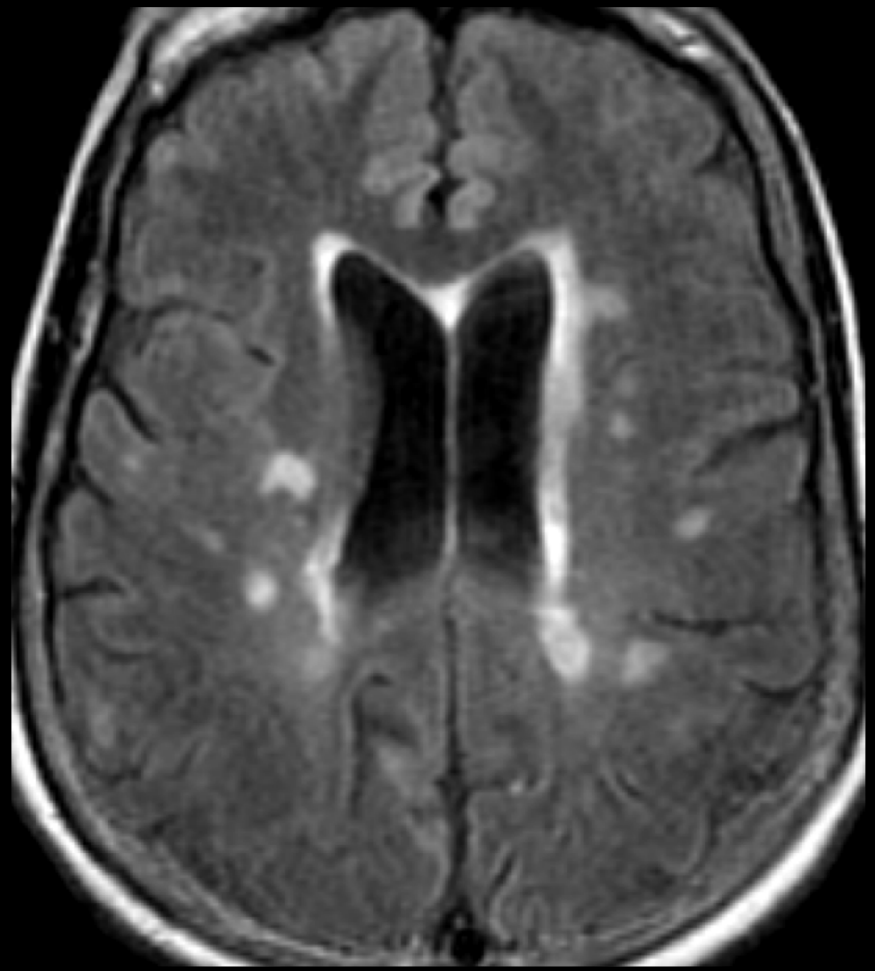
www.thelancet.com/neurology **Published online September 29, 2017** **http://dx.doi.org/10.1016/S1474-4422(17)30282-X**

Up to 10% risk/year
in year 6
if JCV index >1.5

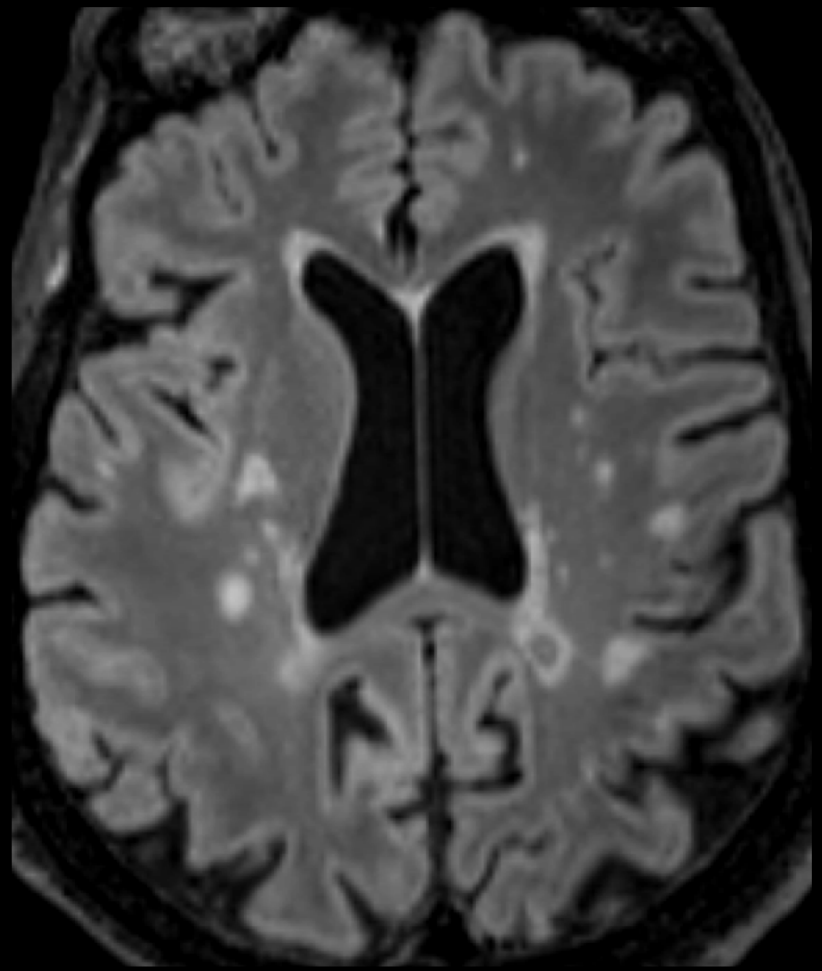


Number at risk*							
No previous immunosuppressant use	18 616	16 130	12 925	9755	6880	4379	2277
Previous immunosuppressant use	3080	2671	2201	1693	1159	720	366
Cumulative number of patients with PML†							
No previous immunosuppressant use	0	2	10	28	62	89	109
Previous immunosuppressant use	0	1	2	9	21	29	32

PPMS... treated with natalizumab



age 63



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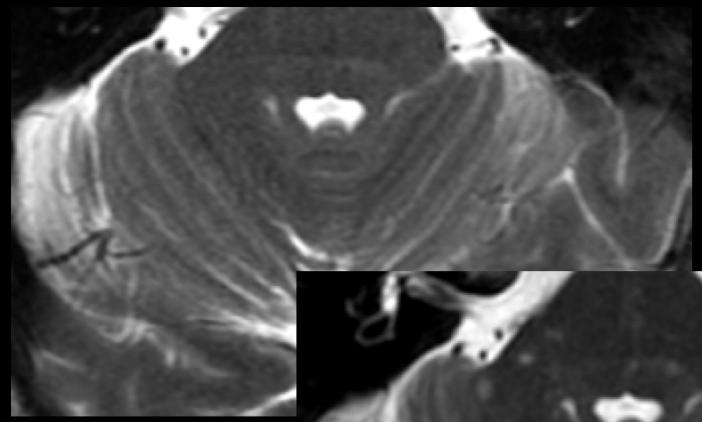
age 65

Infratentorial PML



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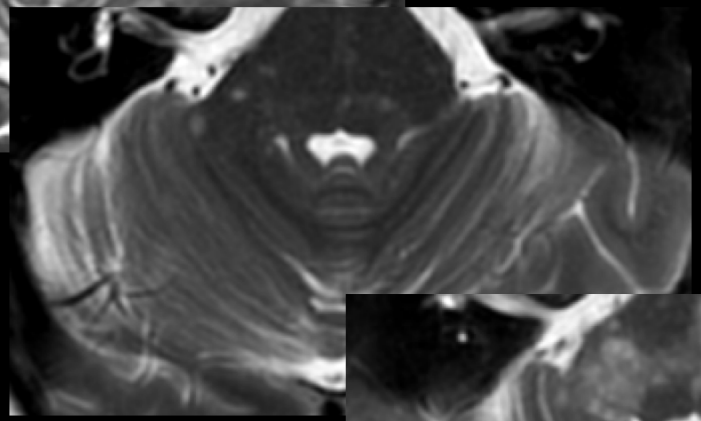

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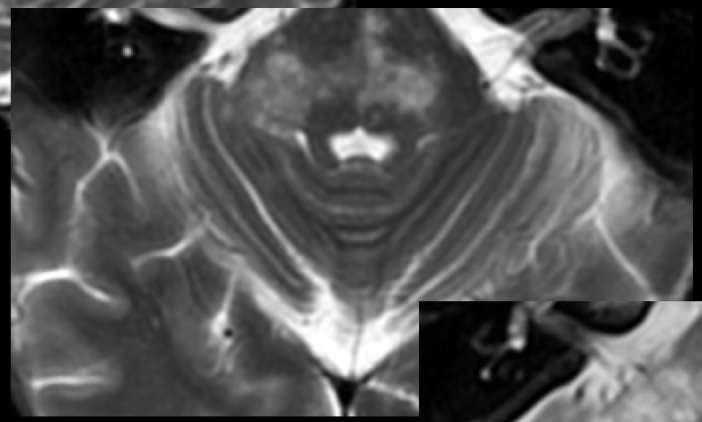

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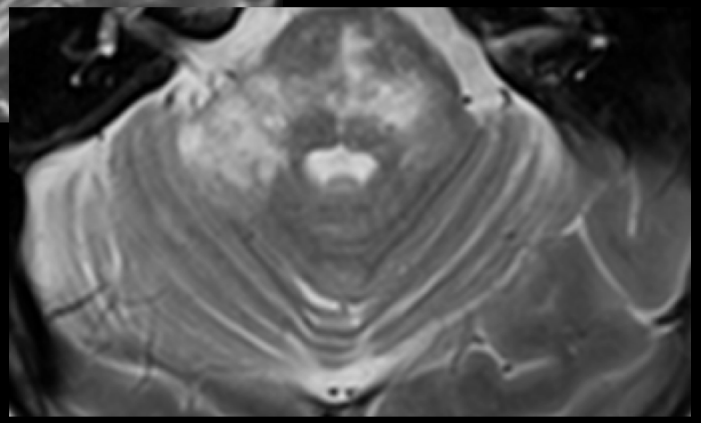

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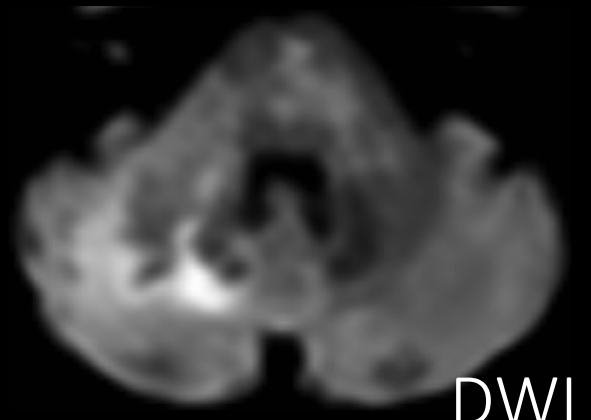
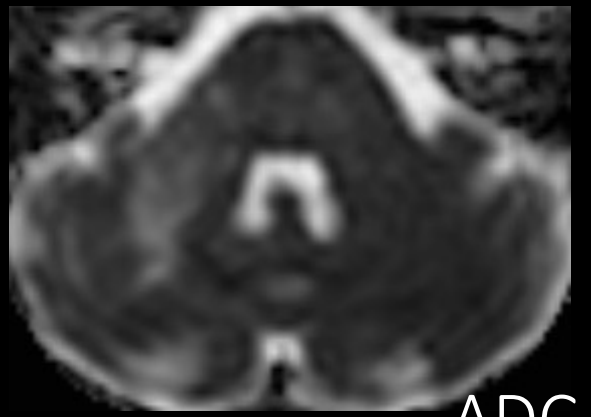
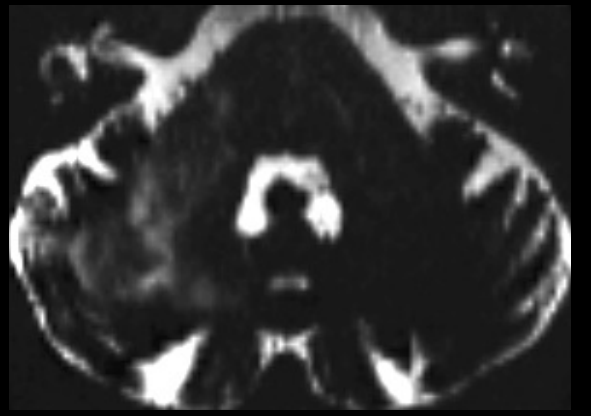


DWI



ADC

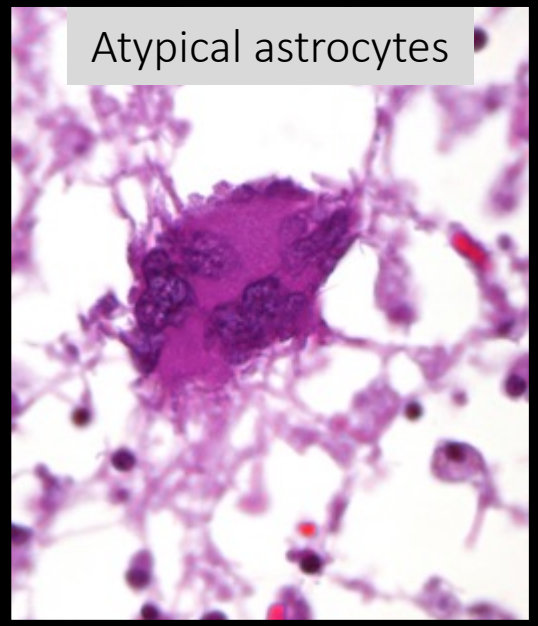


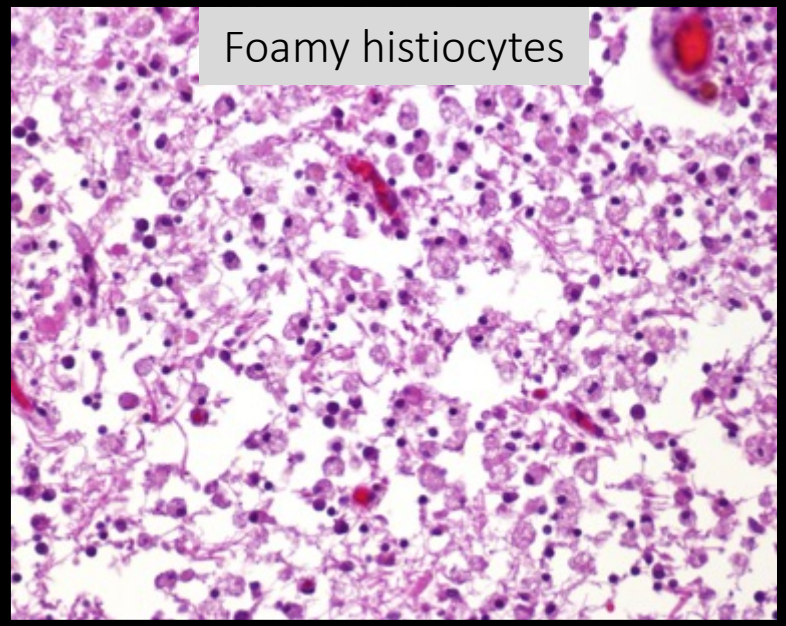
Free Water

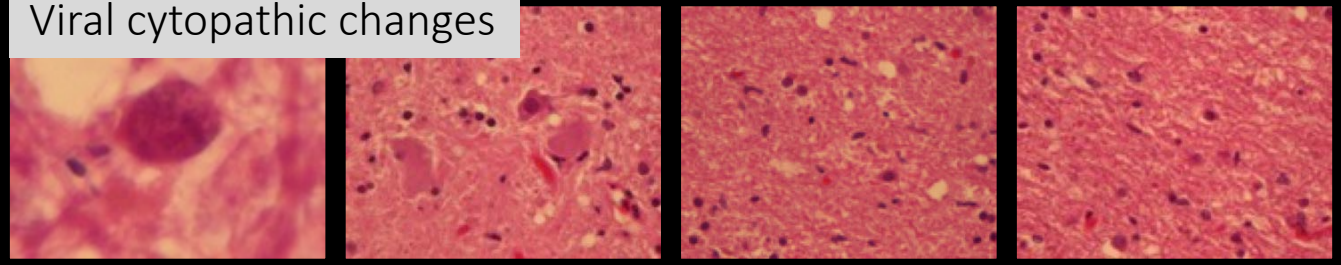
CSF – 221,729 copies/ml of JCV DNA

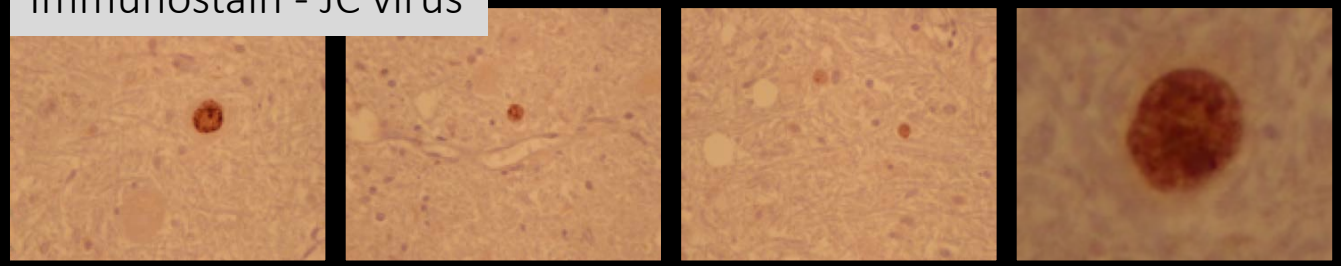
Plasma – 91 copies/ml of JCV DNA

PML Pathology

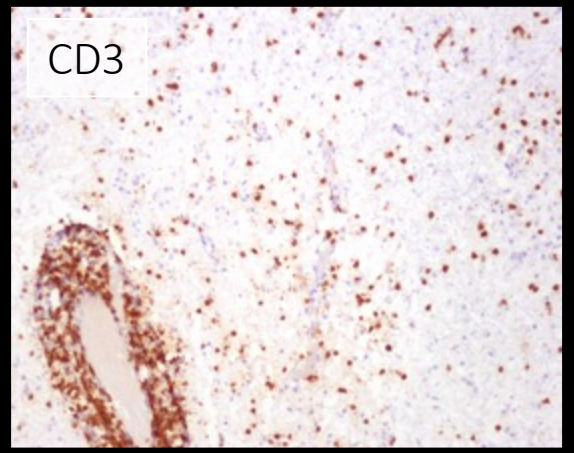


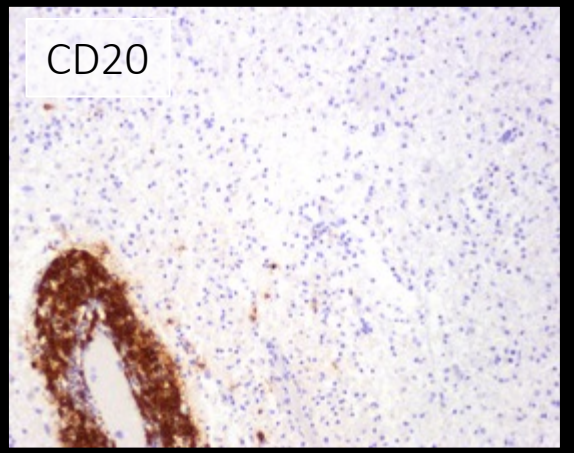


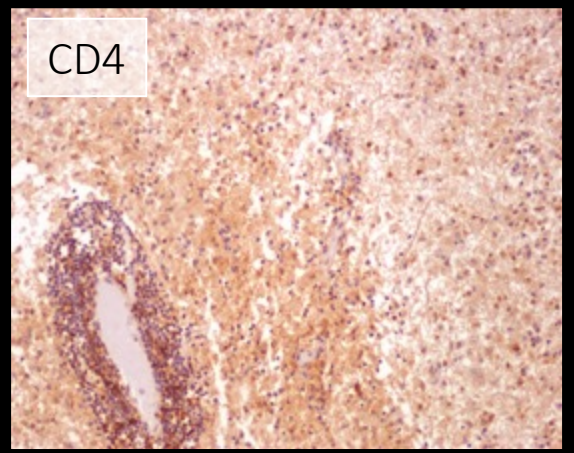


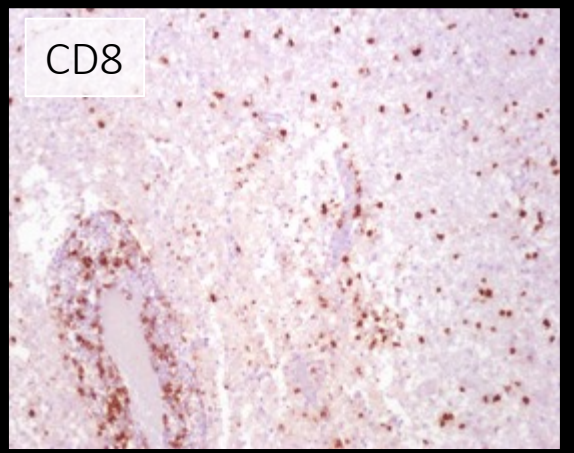


Immune Reconstitution Inflammation









Salient features of PML

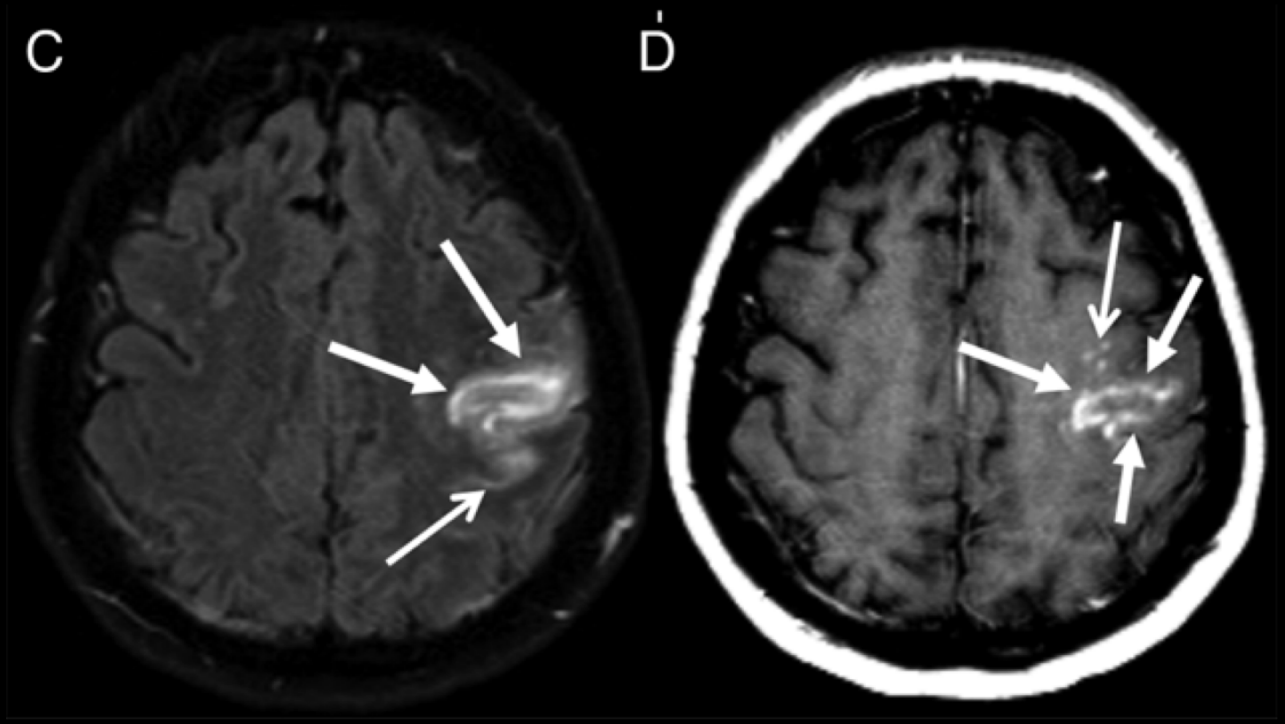
Clinical

- cognitive slowing
- progressive weakness
- gait abnormality
- visual field cuts
- aphasia
- incoordination

Radiological

- lesions are irregular & can be large; punctate also common
- supratentorial or infratentorial
- signal: T2 bright, T1 dark
- peripheral restricted diffusion
- variable enhancement (patchy or punctate)
- paramagnetic leukocortical band: late

PML-IRIS



- in natalizumab PML, punctate or patchy enhancement of the PML lesion suggests IRIS
- but consider necrosis, MS rebound
- treating vs. watching: tricky balance

Multiple sclerosis

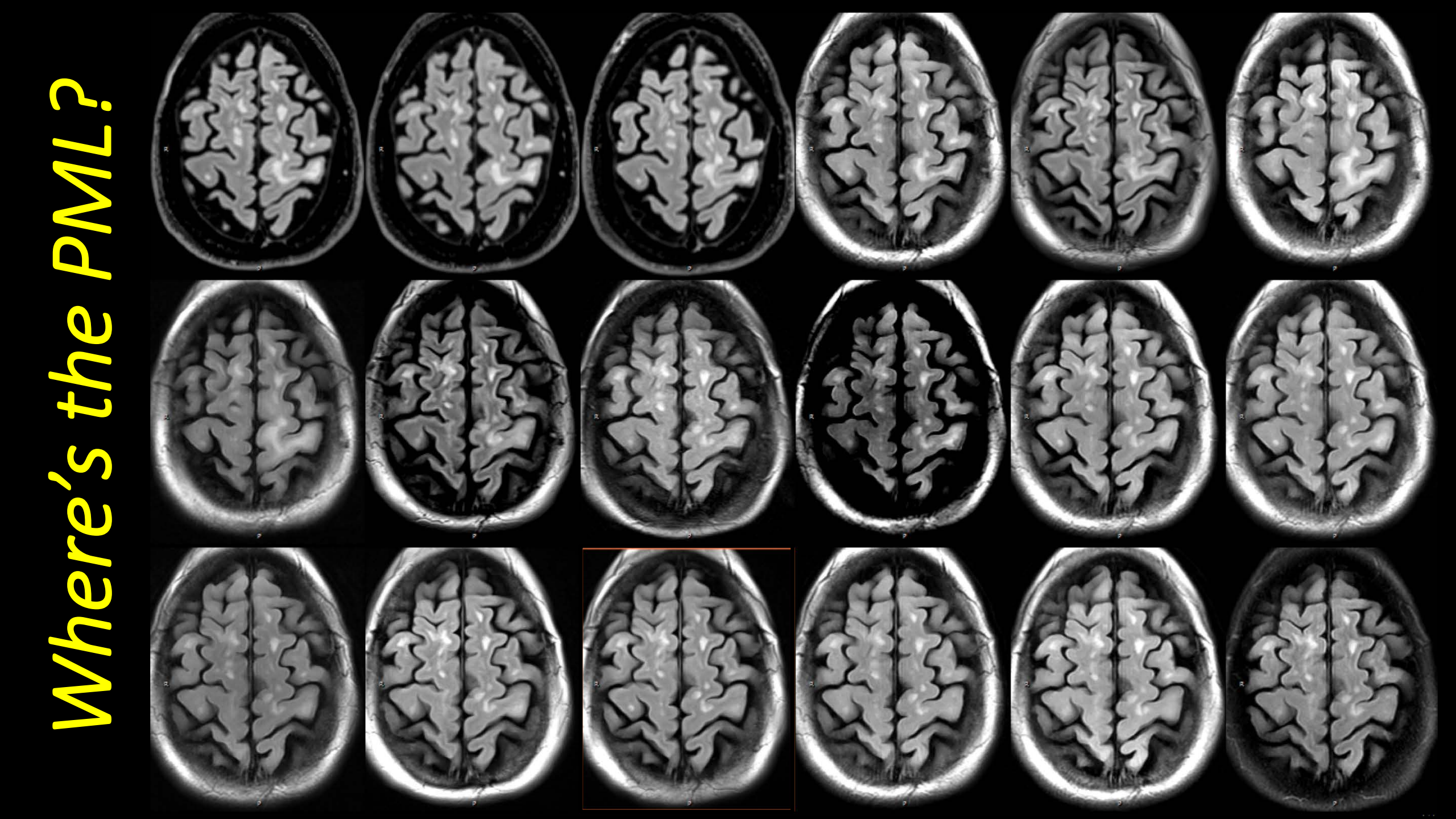
RESEARCH PAPER

MRI characteristics of early PML-IRIS after natalizumab treatment in patients with MS

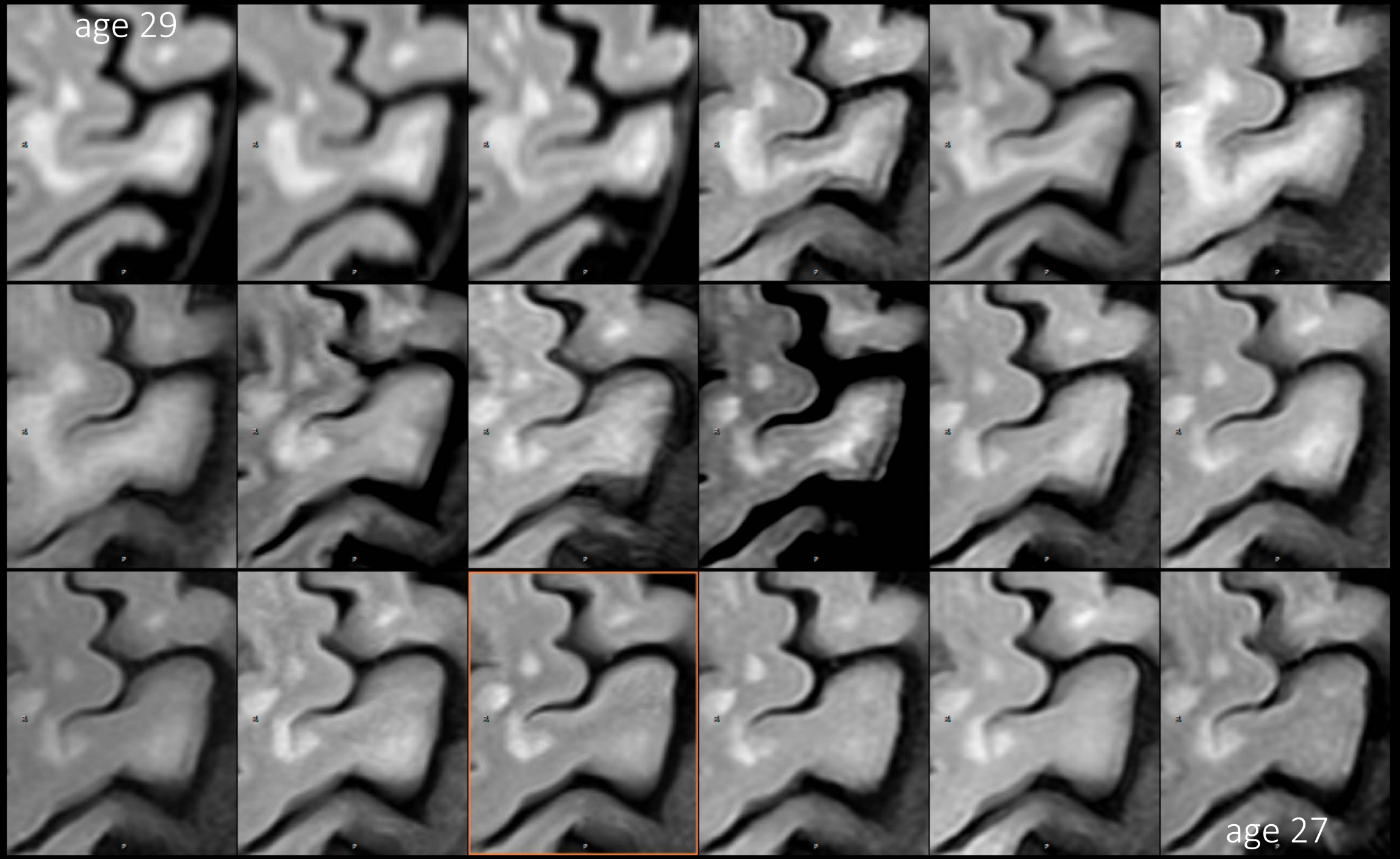
Mike P Wattjes,[1,2] Martijn T Wijburg,[1,2,3] Anke Vennegoor,[1,3] Birgit I Witte,[4] Marlieke de Vos,[1,2] Nancy D Richert,[5] Bernard M J Uitdehaag,[1,3] Frederik Barkhof,[1,2] Joep Killestein,[1,3] on behalf of the Dutch-Belgian Natalizumab-associated PML study group

Table 3 Imaging characteristics of early PML-IRIS

	Number of patients (%)
Mass effect	10 (38.5)*
Signs of oedema	7 (26.9)*
Perivascular T2 lesions	9 (34.6)*
Contrast-enhancing lesions	24 (92.3)*
Localisation of contrast enhancement	
In the centre of PML lesions	4 (16.7)†
In the border of PML lesions	23 (95.8)†
Outside of PML lesions‡	3 (12.5)†
Punctuate perivascular enhancement§	8 (33.3)†
Pattern of contrast enhancement¶	
Punctate	11 (45.8)†
Homogeneous	0 (0)†
Patchy	17 (70.8)†
Signs of meningeal inflammation	0 (0)*


Where's the PML?

Where's the PML?



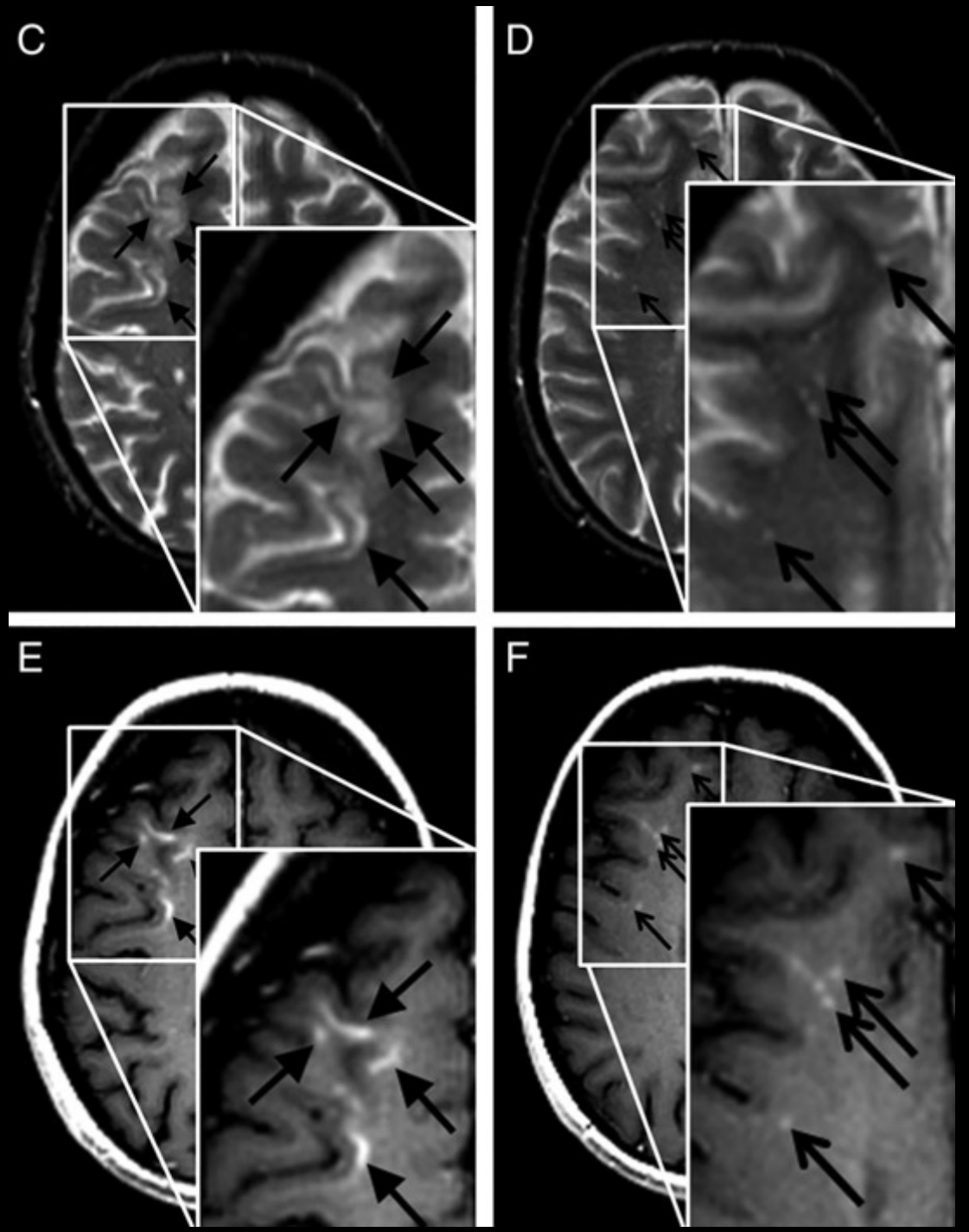
MRI criteria differentiating asymptomatic PML from new MS lesions during natalizumab pharmacovigilance

Martijn T Wijburg,[1,2] Birgit I Witte,[3] Anke Vennegoor,[1] Stefan D Roosendaal,[2,4] Esther Sanchez,[2] Yaou Liu,[2,5] Carine O Martins Jarnalo,[2,6] Bernard MJ Uitdehaag,[1] Frederik Barkhof,[2] Joep Killestein,[1] Mike P Wattjes[2]

J Neurol Neurosurg Psychiatry 2016;**87**:1138–1145. doi:10.1136/jnnp-2016-313772

Table 2 Multivariable prediction model of lesion characteristics differentiating asymptomatic PML from new MS lesions in order of entry in the model

Predictive lesion characteristics*	OR for PML†	95% CI	p Value
Focal lesion appearance‡	0.009	0.0008 to 0.12	<0.001
Periventricular white matter localisation	0.0006	0.00003 to 0.0121	<0.001
Presence of punctate T2 lesions§	183.2	11.4 to 2950.7	<0.001
Cortical grey matter involvement	59.8	8.4 to 427.6	<0.001

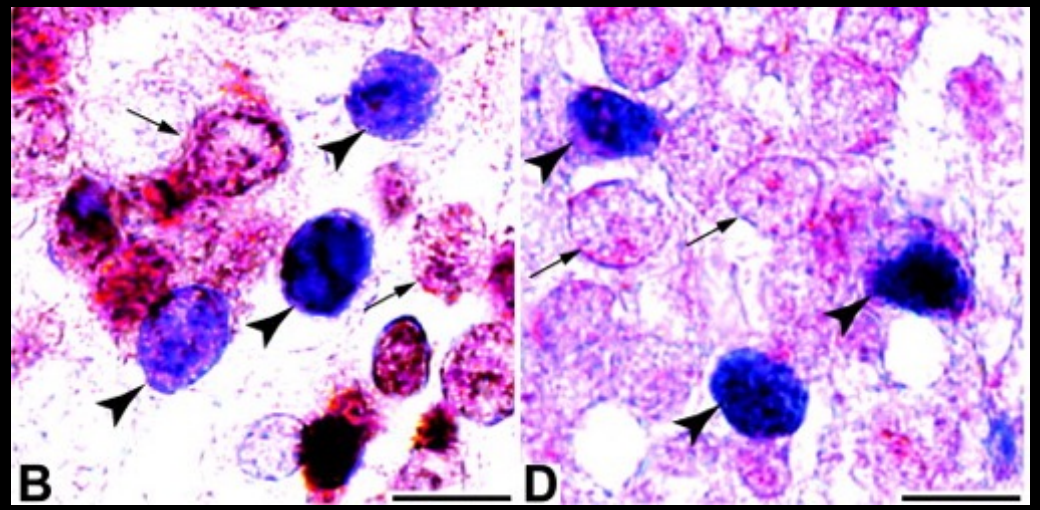


J Neurol (2016) 263:649–656
DOI 10.1007/s00415-015-8001-3

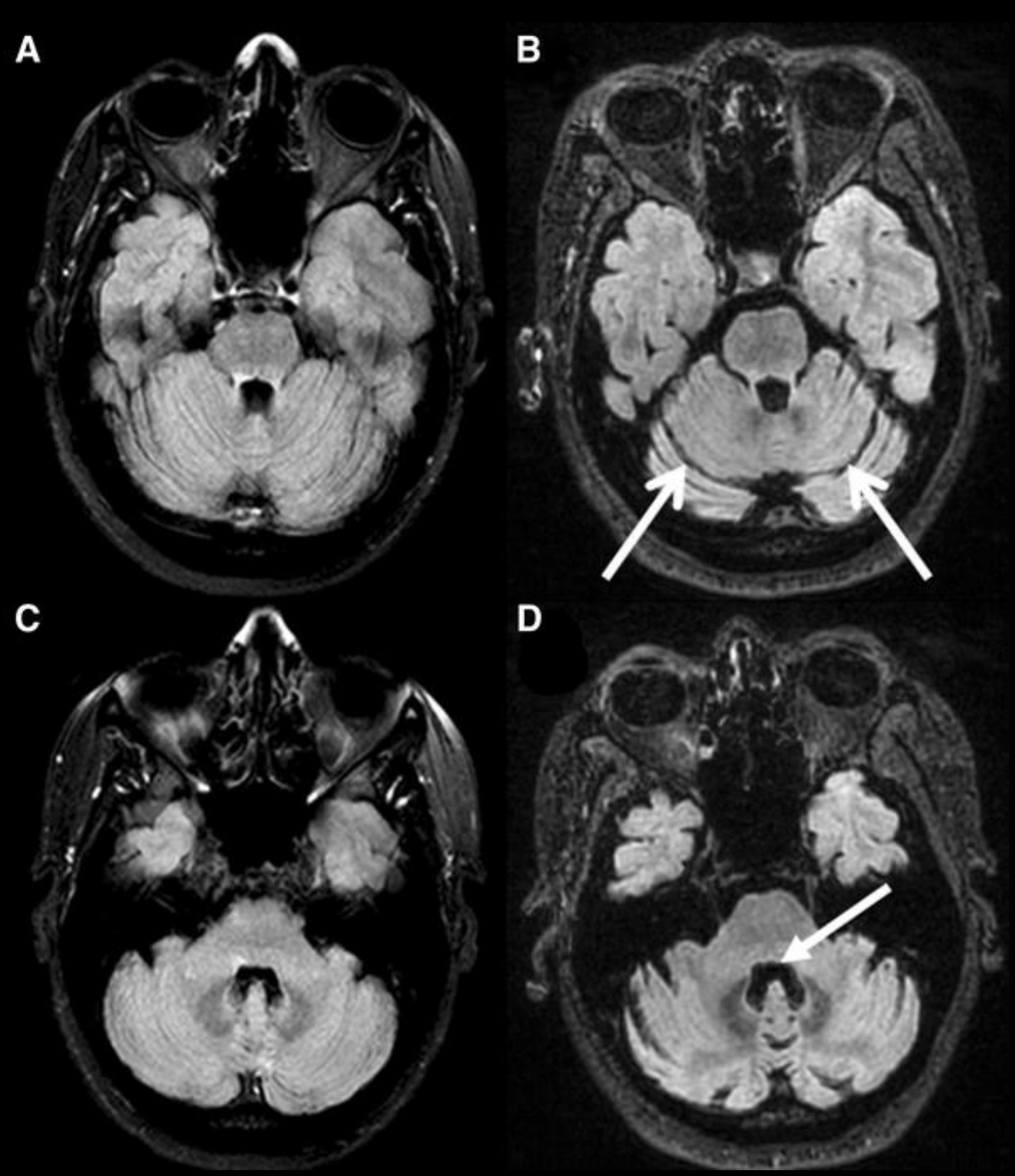
ORIGINAL COMMUNICATION

Concomitant granule cell neuronopathy in patients with natalizumab-associated PML

Martijn T. Wijburg[1,2] · Dorine Siepman[3] · Jeroen J. J. van Eijk[4] · Joep Killestein[1] · Mike P. Wattjes[2]

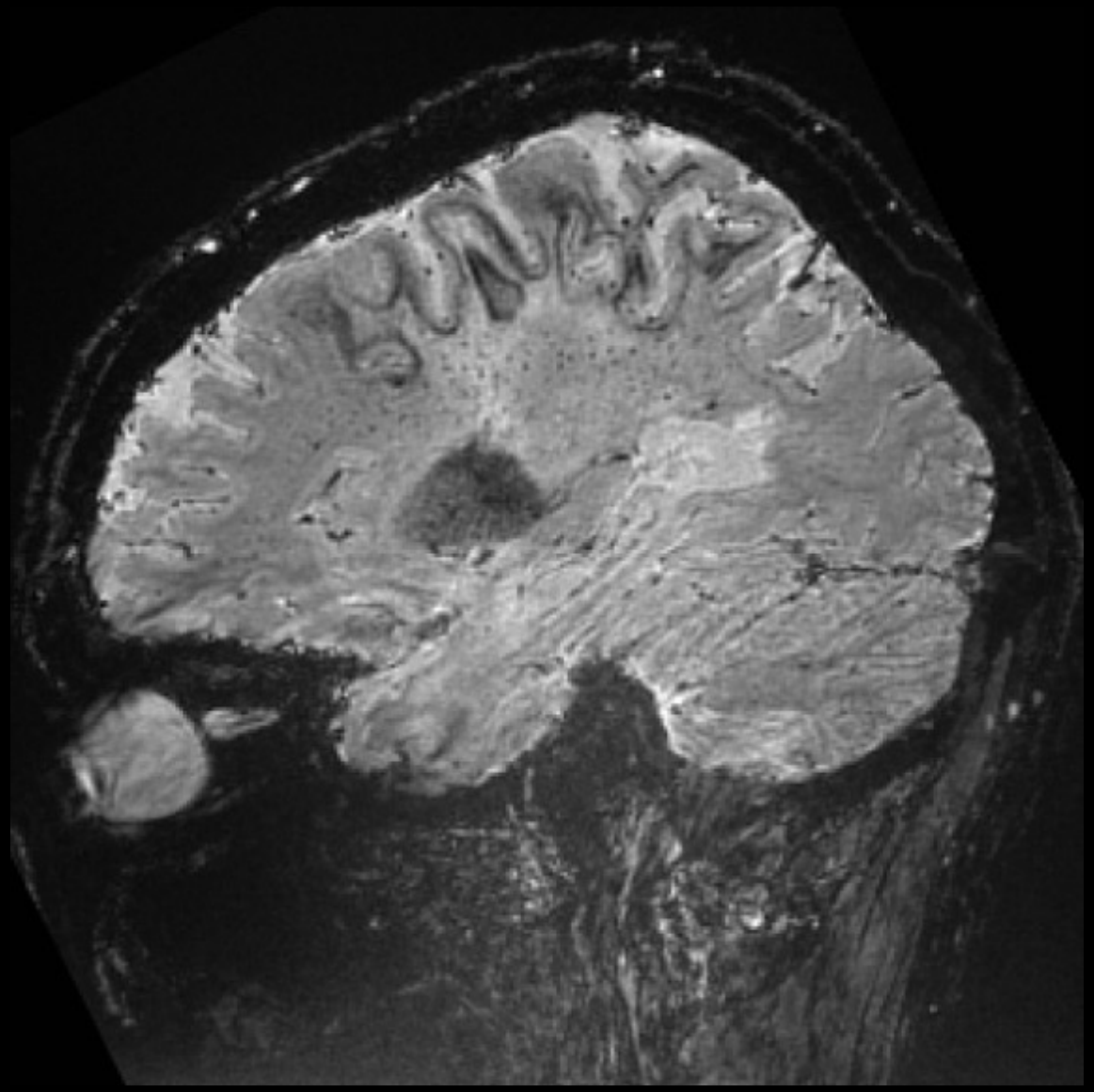


Koralnik et al., Ann Neurol 2005 (10.1002/ana.20431)

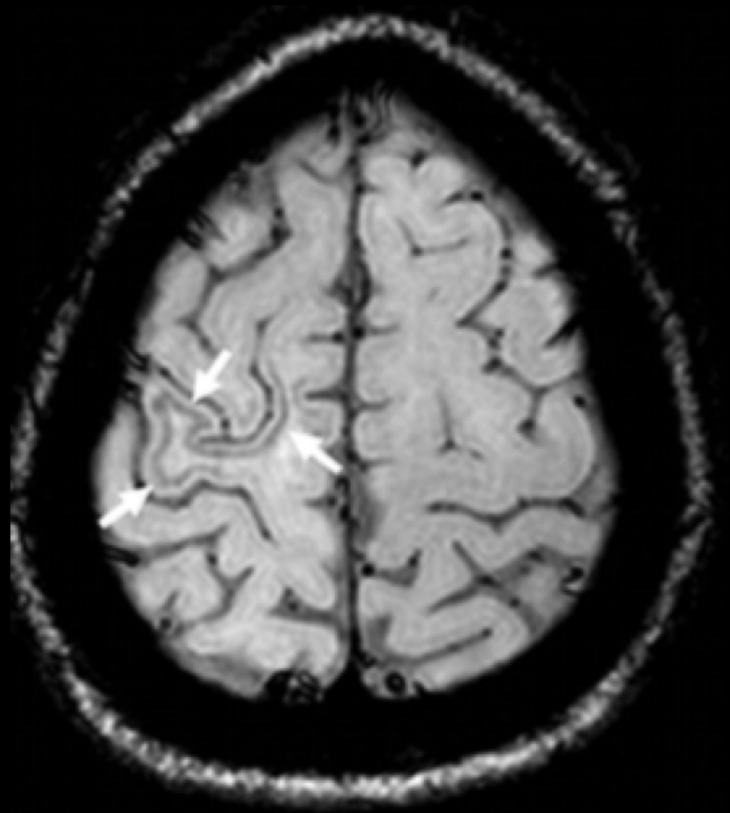


See also: Schippling et al., Ann Neurol 2013 (10.1002/ana.23973)

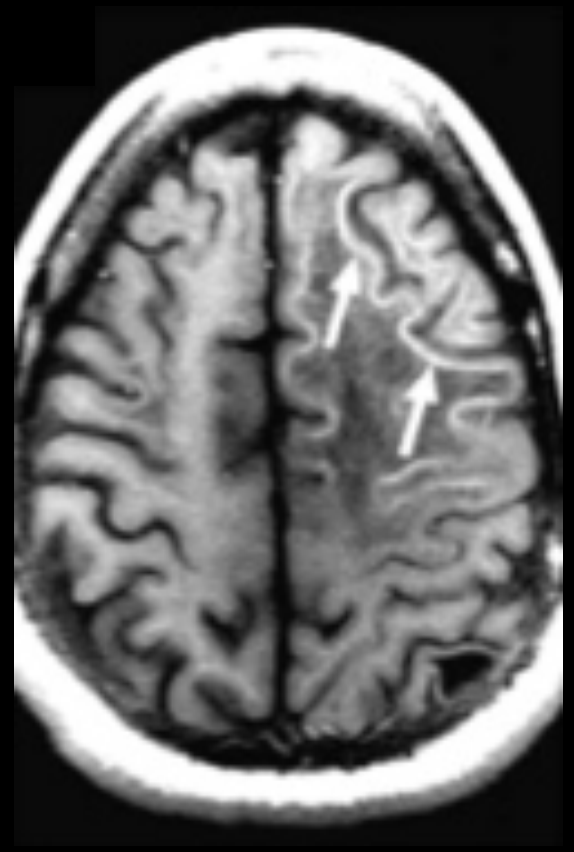
Paramagnetic Leukocortical Band in PML



Sethi et al., ECTRIMS 2014



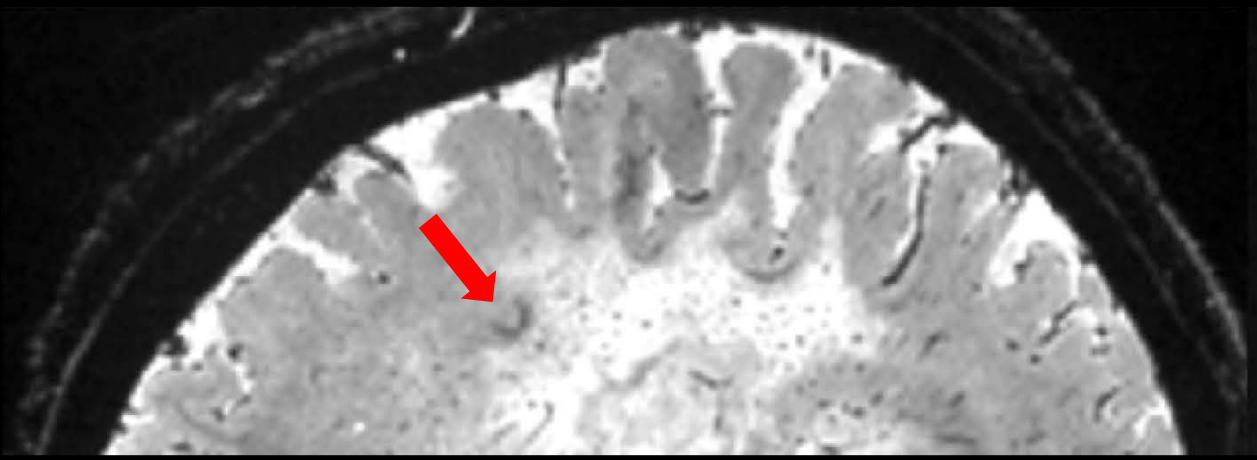
Susceptibility-weighted
Hodel et al. 2015



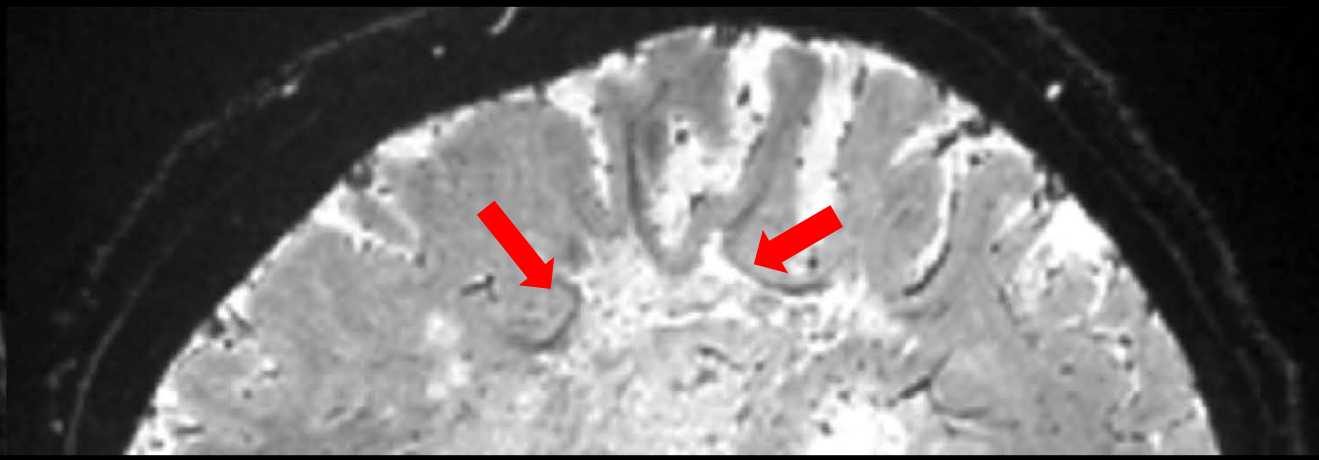
T1 spin echo
Khoury et al 2014

Characteristics of the Paramagnetic Band

- spans the gray/white junction, involves deeper cortical layers
- infratentorial PML: dentate nucleus or cerebellar cortex
- expands as the PML lesion enlarges but *lags behind*
- persists & intensifies after PML lesion peaks and begins to involute



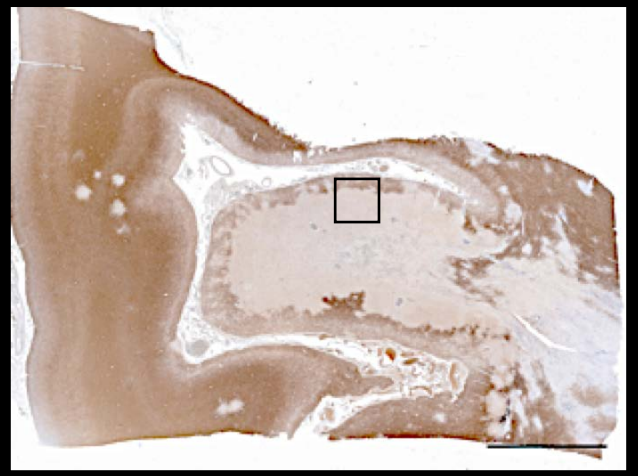
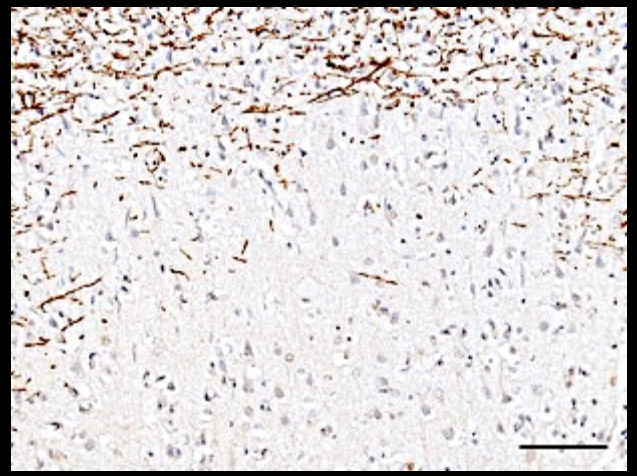
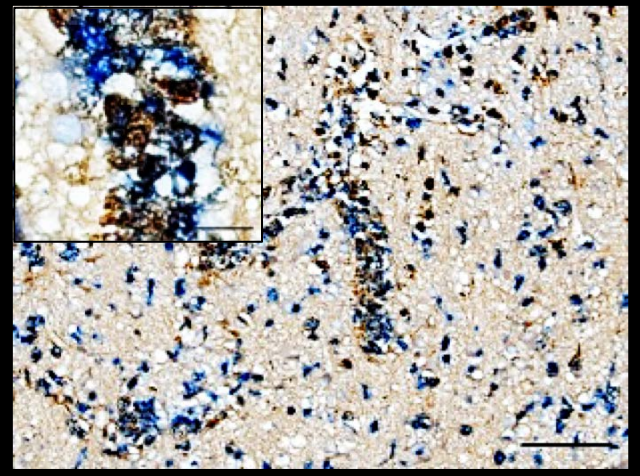
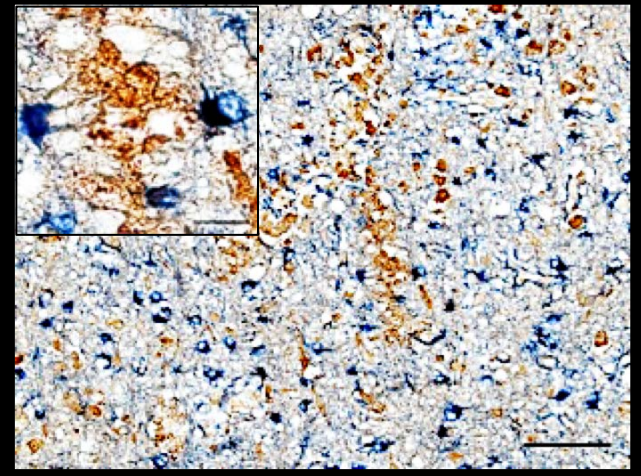
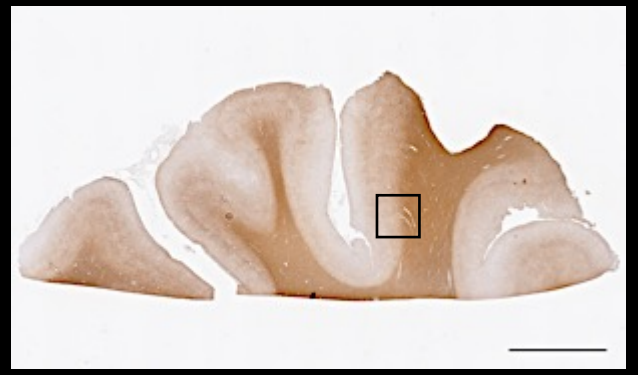
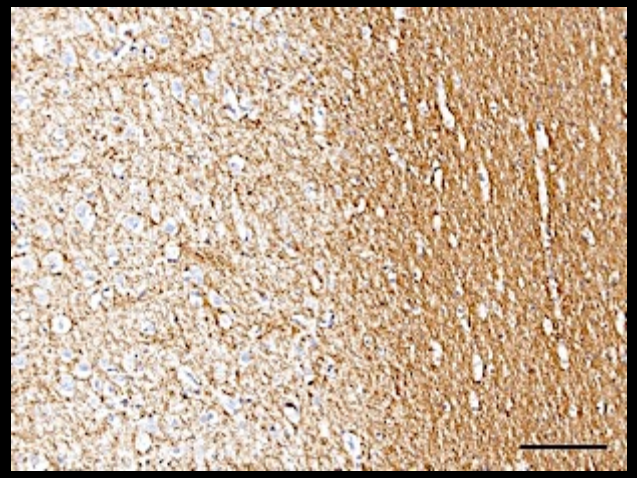
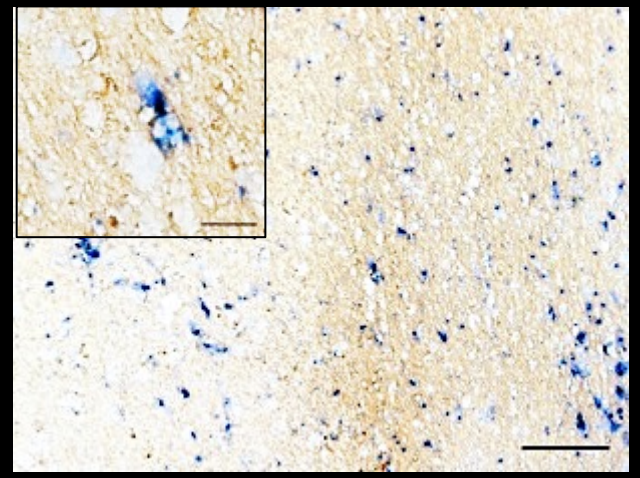
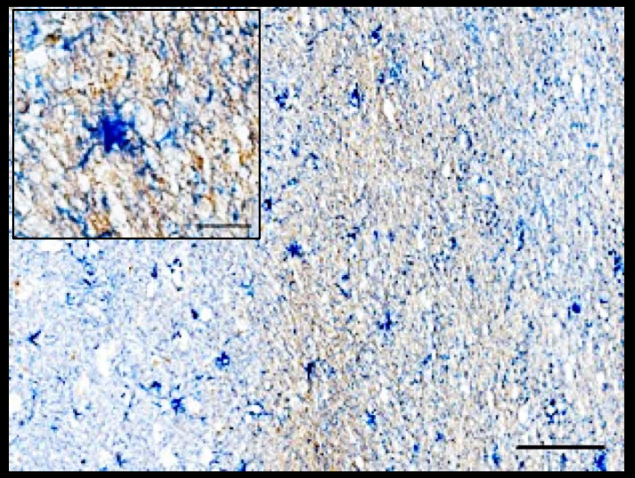
Baseline



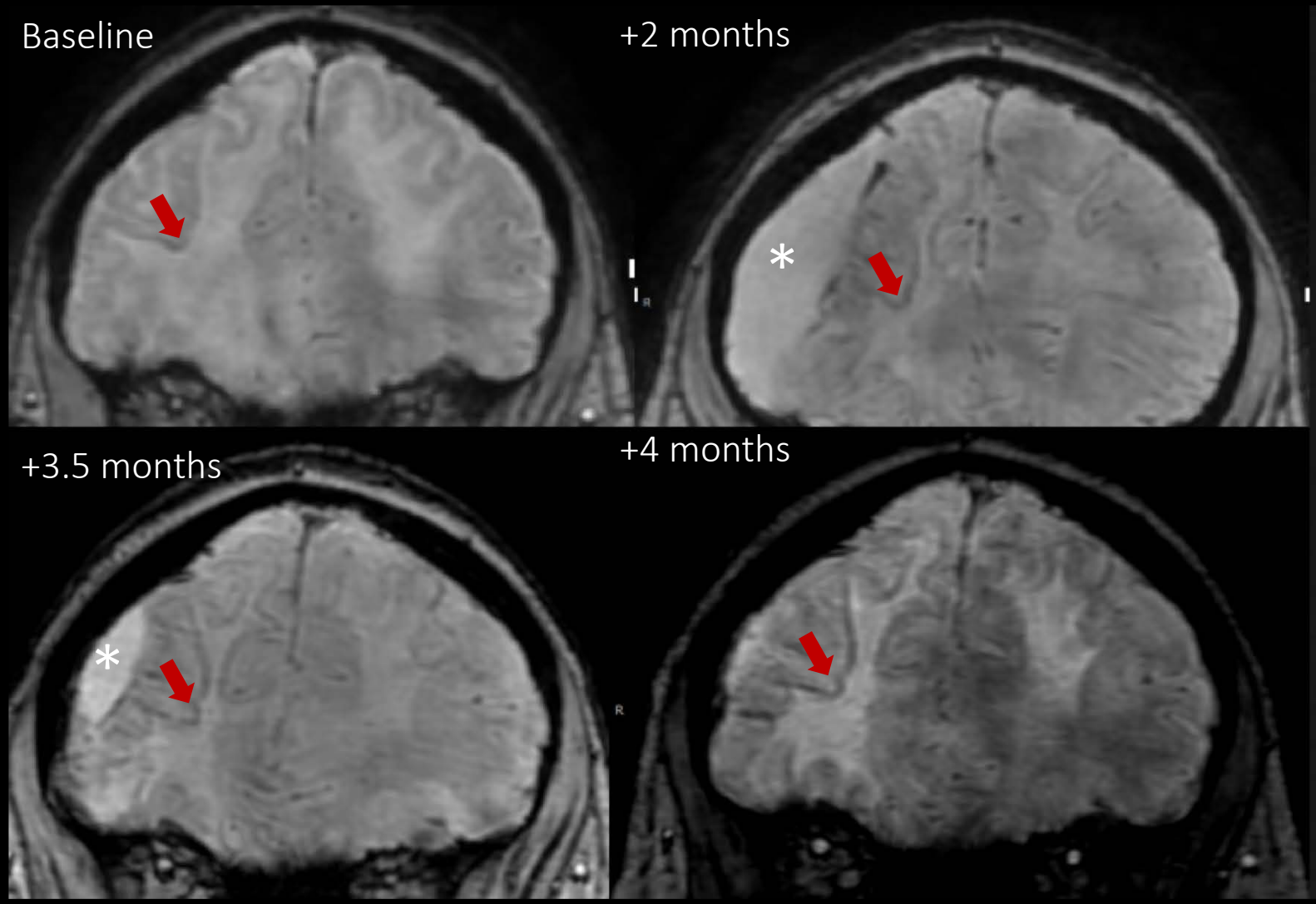
+4 months

Paramagnetic band: iron in macrophages/microglia

PLP *PLP* *Iron/CD68* *Iron/GFAP*

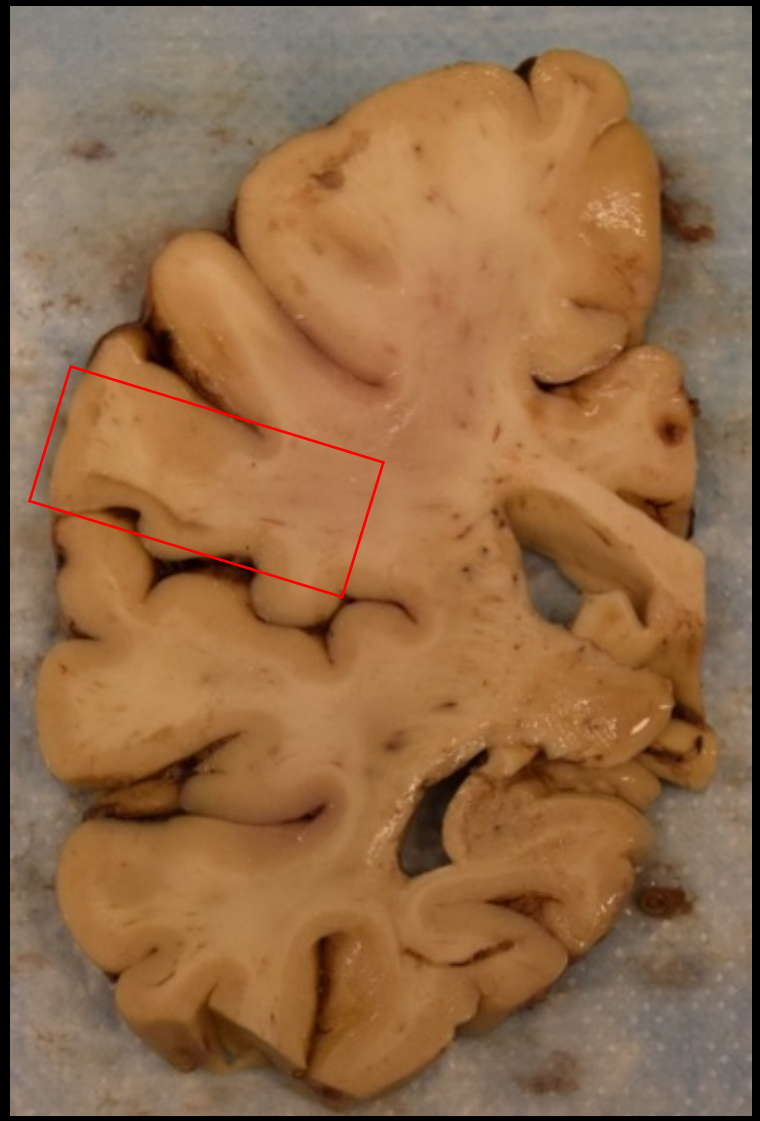









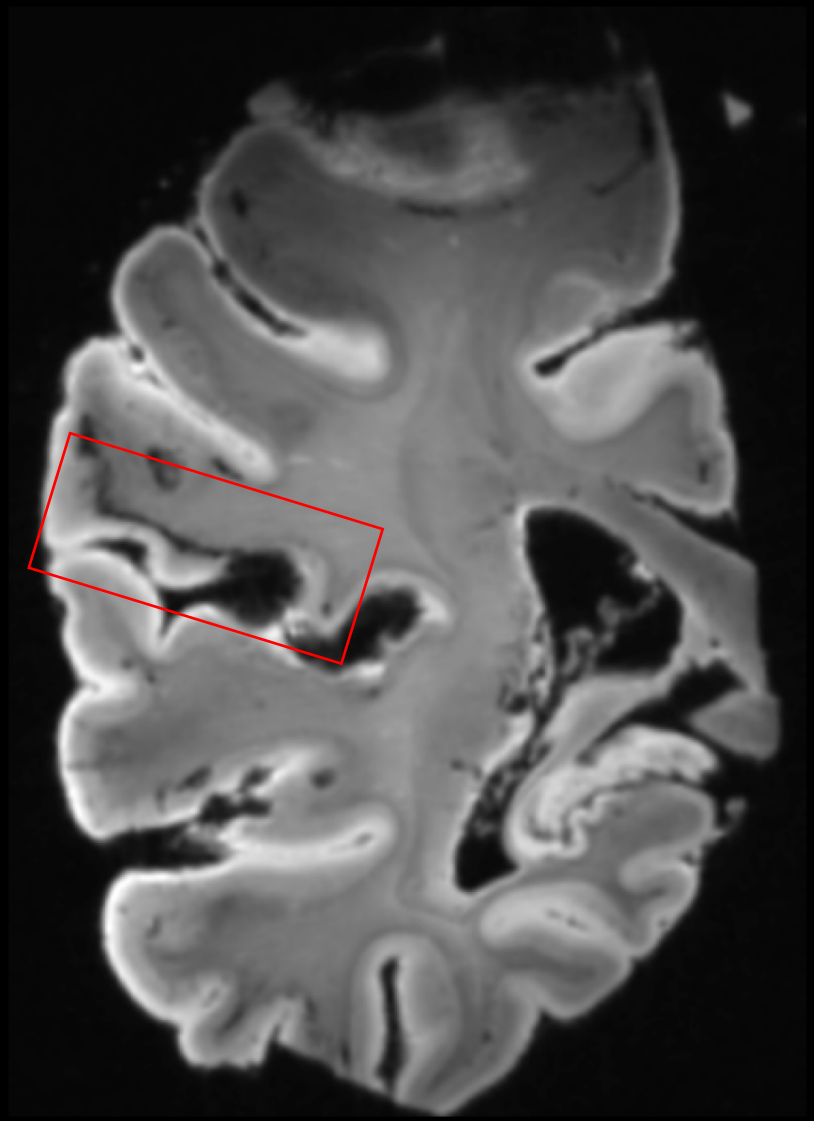
Unique Case: In Vivo to Postmortem

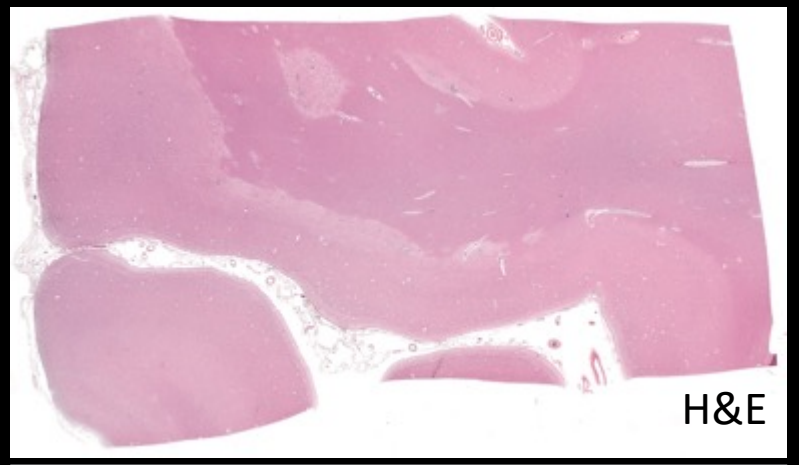


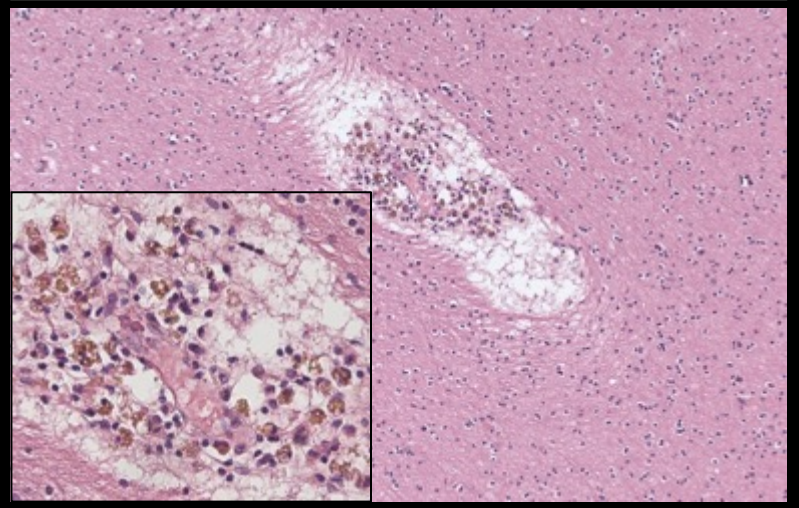
Sethi et al., in preparation

Pseudolaminar Necrosis

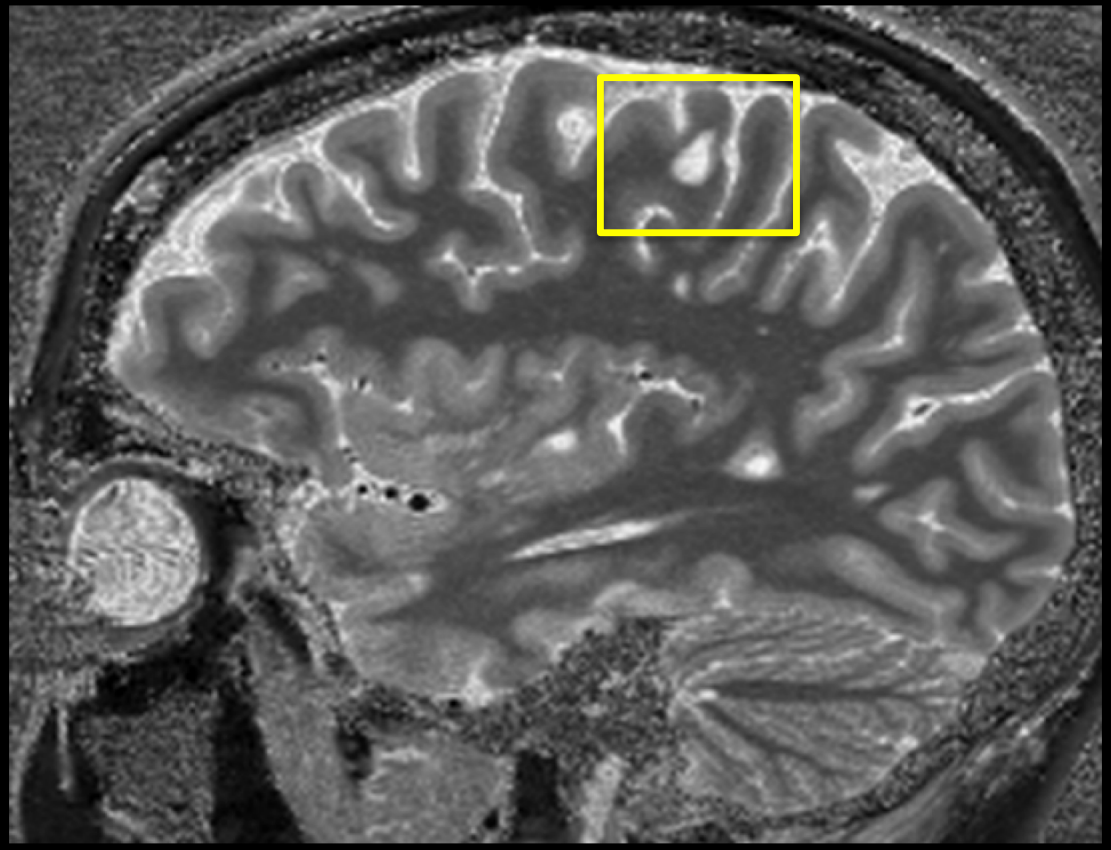


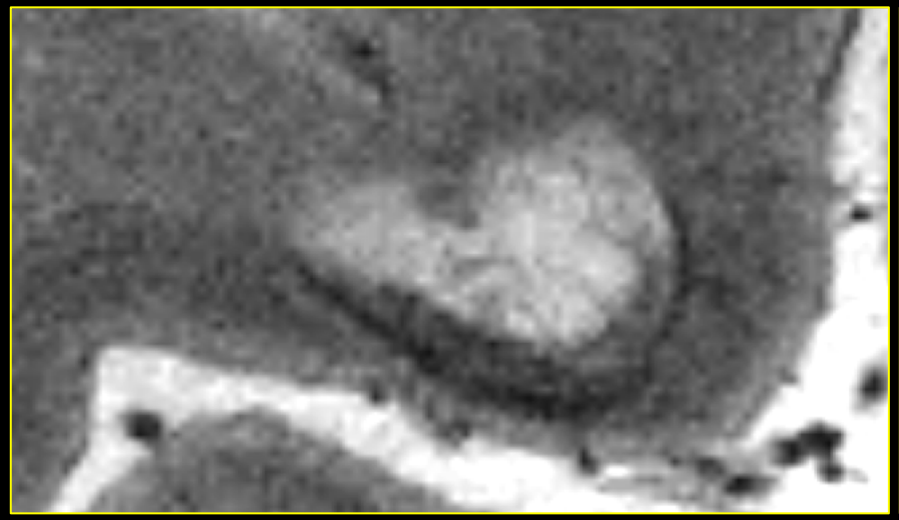


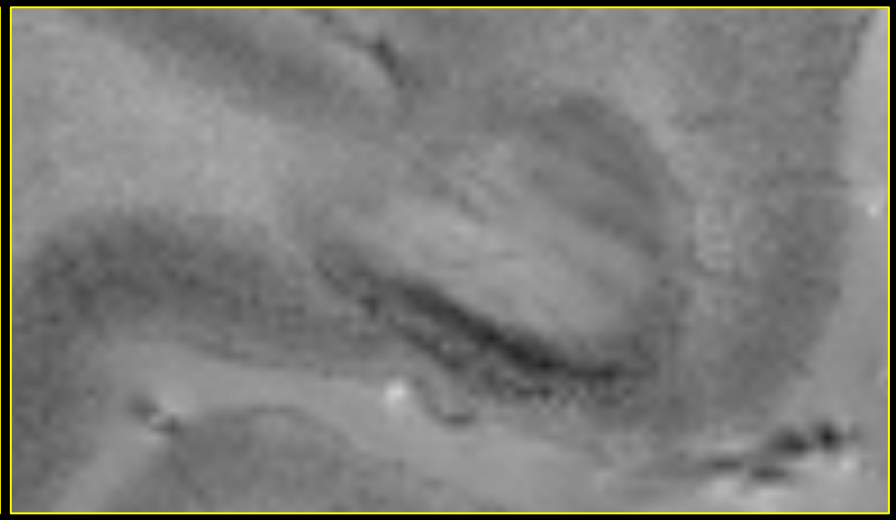




Sometimes Seen in MS!







Sethi et al., in preparation

PML Surveillance

Table 1: Frequency of MRI surveillance

Clinical Indication	Frequency of Imaging	Imaging Protocol
RRMS, routine surveillance	Annually for at least the first 2 or 3 years after starting therapy or switching DMT	T2-weighted and contrast-enhanced T1-weighted
Higher risk patients (positive for JC virus serum antibodies) with >24 mo of NTZ exposure	Every 3–6 months	T2WI, T2 FLAIR, DWI, SWI (if indicated)
Low risk of PML (negative for JC virus serum antibodies)	Annually	T2WI, T2 FLAIR, DWI, SWI (if indicated)
Patients at high risk of developing opportunistic infections who are switching DMT	MRI when the current treatment is discontinued and 3–6 months after the new treatment is started	T2WI, T2 FLAIR, DWI, SWI (if indicated)
Patients who switch from NTZ to other therapeutics (including fingolimod, alemtuzumab, and dimethyl fumarate)	Enhanced pharmacovigilance, including brain MRI every 3–4 mo for up to 12 mo	T2WI, T2 FLAIR, DWI, SWI (if indicated)
Patients who require enhanced pharmacovigilance for other reasons	Every 3–6 mo	As indicated

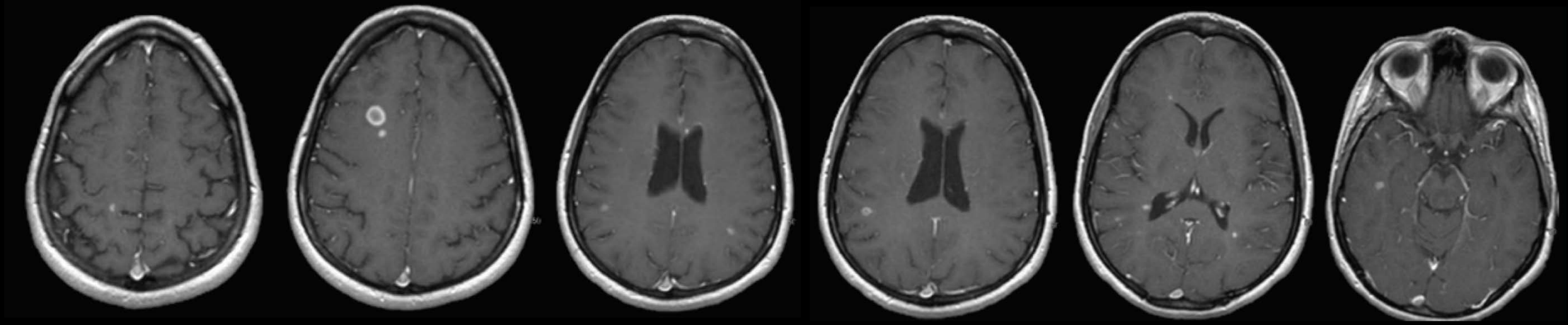
Note:—RRMS indicates relapsing-remitting MS.

McNamara et al., AJNR 2017 (10.3174/ajnr.A5148)

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Tysabri_20/Procedure_started/WC500186688.pdf

Rebound

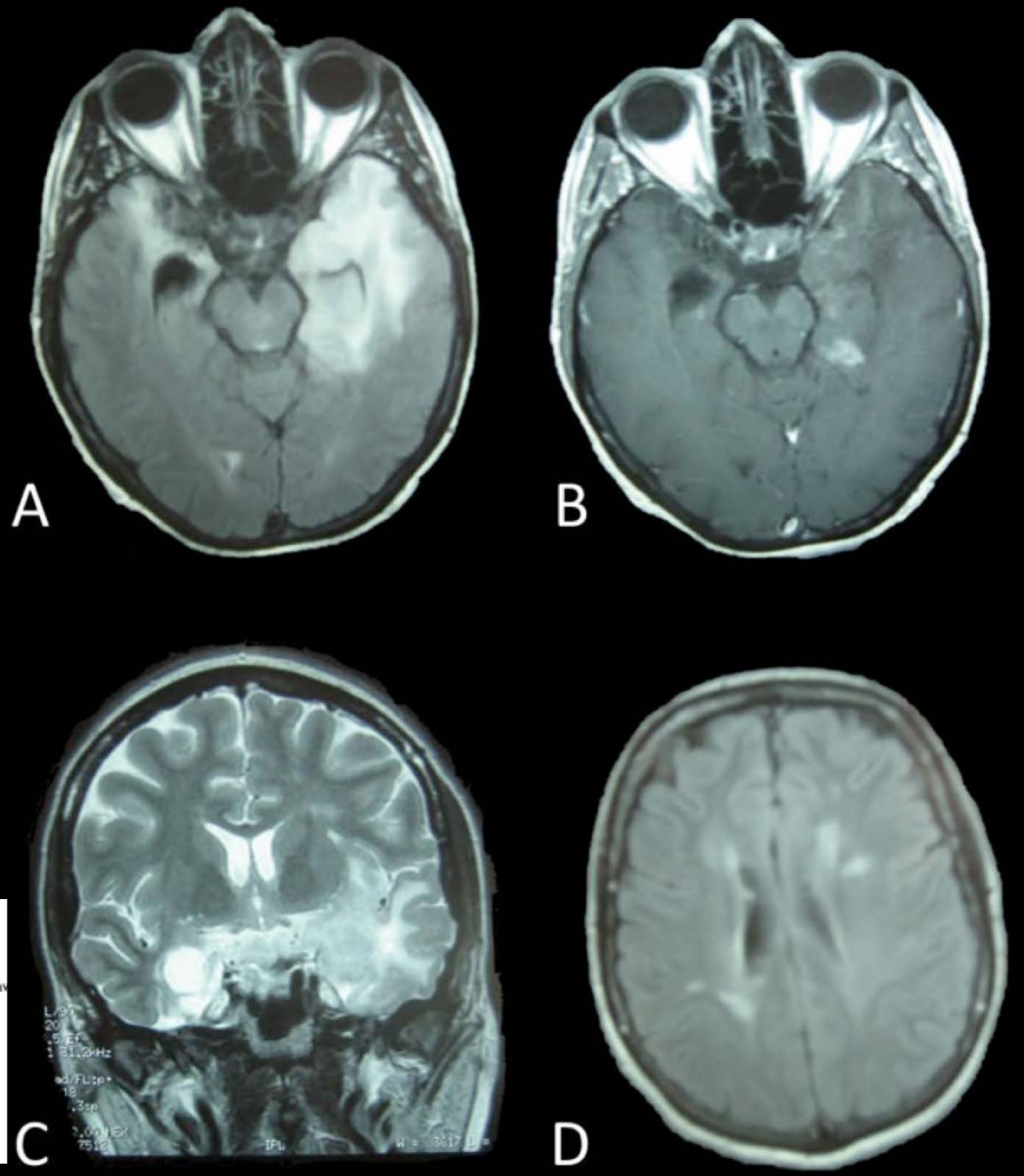
- occurs within 3 months of stopping natalizumab (10-40%) & fingolimod (apparently rarer)
- peripheral autoimmune disease may also recrudesce
- 1 case of fatal rebound: extensive infiltration of CD8 T cells, B cells, antibody, complement (immunopattern II) (Larochelle et al. 2017)
- discontinuation of highly active therapy needs to be managed carefully



Honce et al., *MS International* 2015 (10.1155/2015/809252)

HSV encephalitis

- typically affects limbic system, medial temporal lobes, inferomedial frontal lobes, insula
- parenchymal & leptomeningeal gadolinium enhancement
- restricted diffusion
- hemorrhage is common



Herpes encephalitis during natalizumab treatment in multiple sclerosis

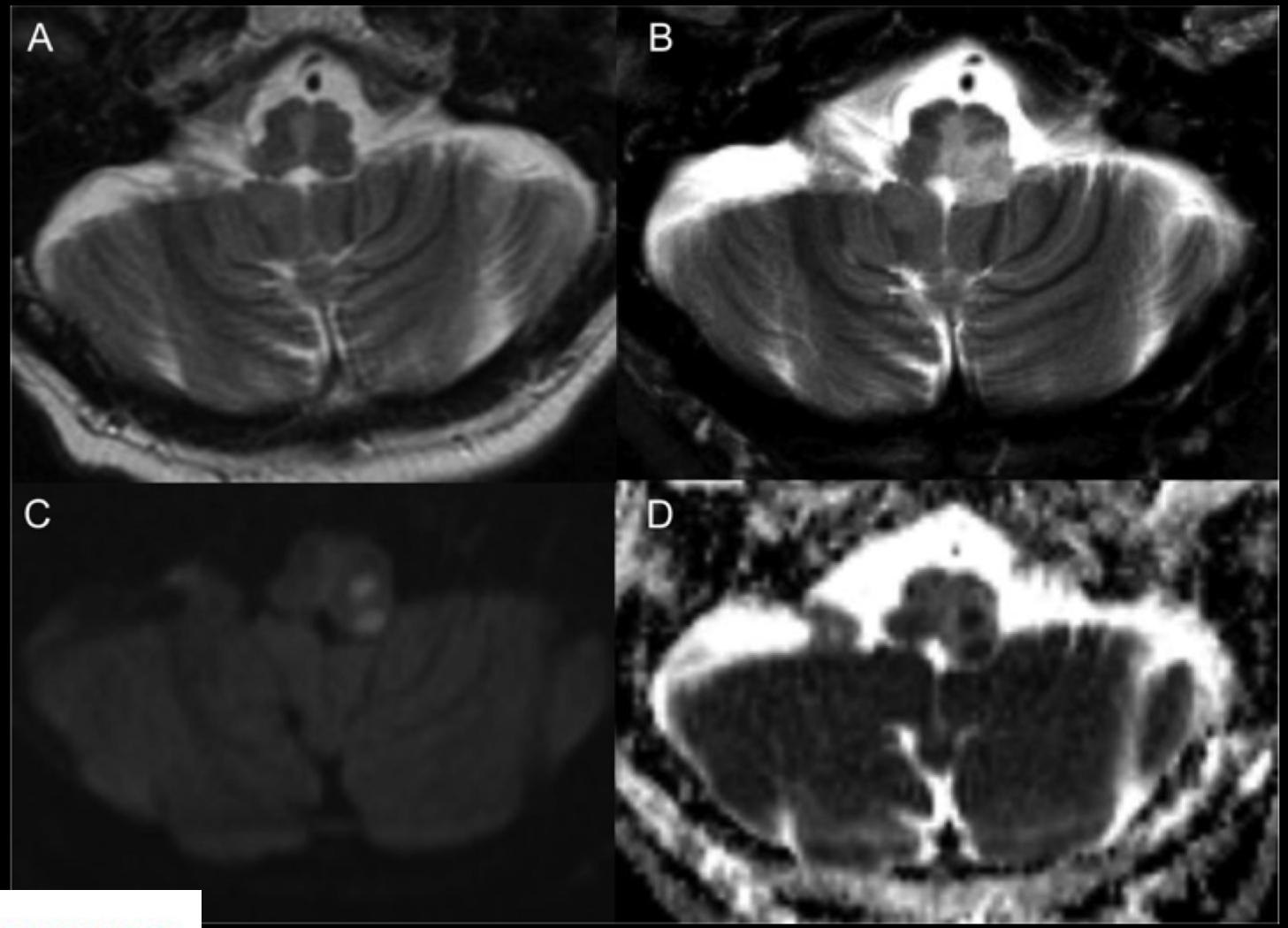
A Kwiatkowski, J Gallois, N Bilbault, G Calais, A Mackowiak and P Hautecoeur

Multiple Sclerosis Journal
18(6) 909–911

DOI: 10.1177/1352458511428082
msj.sagepub.com
SAGE

VZV vasculitis

- stroke (ischemic & hemorrhagic)
- hemorrhage (subarachnoid & parenchymal)
- segmental arterial constriction & dilatation (“beading”)
- can result in arterial dissection
- association with giant cell arteritis



John N. Ratchford, MD*
Kathleen Costello, MS, ANP-BC, MSCN*
Daniel S. Reich, MD, PhD
Peter A. Calabresi, MD

VARICELLA-ZOSTER VIRUS ENCEPHALITIS AND VASCULOPATHY IN A PATIENT TREATED WITH FINGOLIMOD

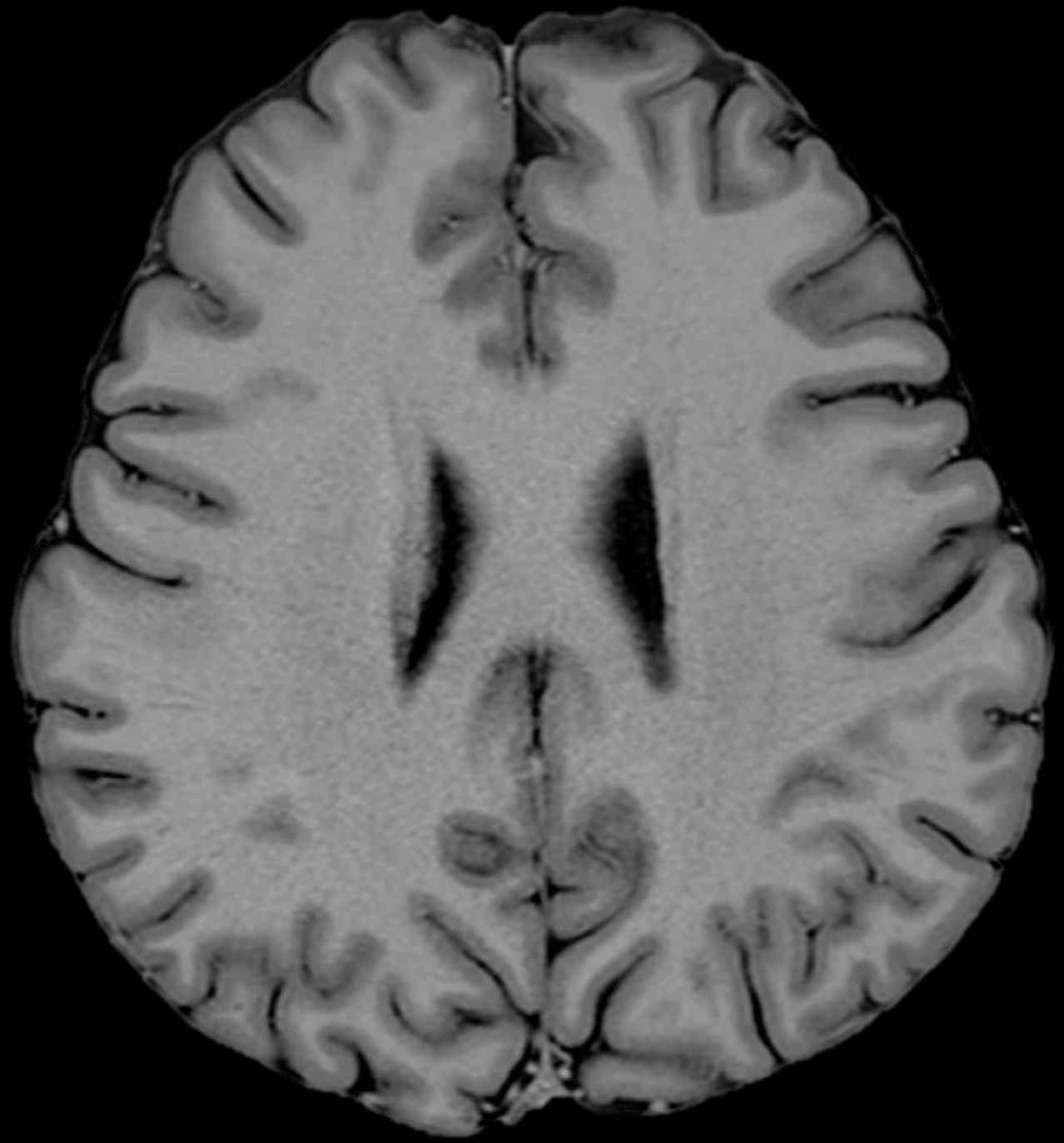
Neurology 79 November 6, 2012

And all the rest

- Depression
- Headache
- Cystoid macular edema
- Reversible cerebral vasoconstriction syndrome (RCVS)
- Hemorrhagic leukoencephalitis
- Primary CNS lymphoma
- Meningitis – aseptic, cryptococcal
- Toxoplasmosis

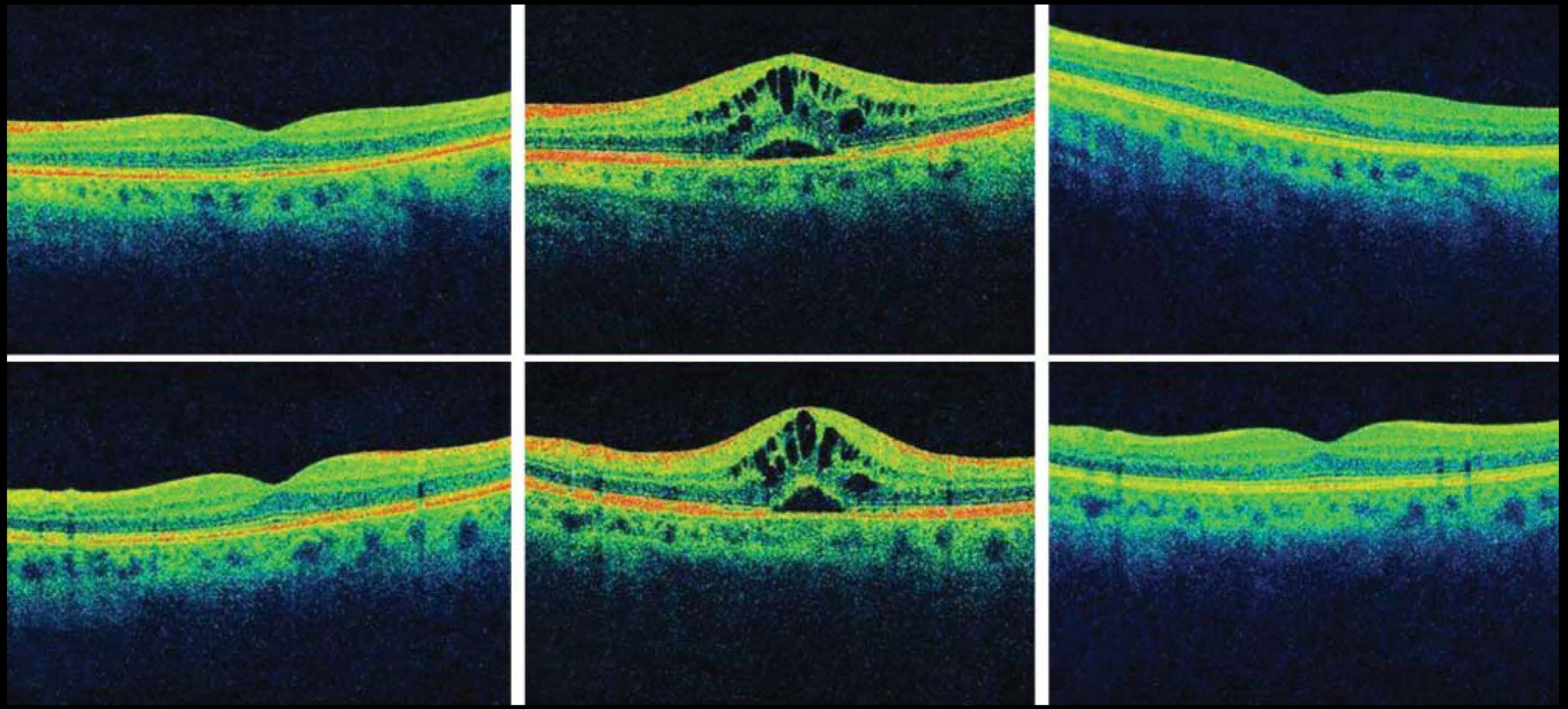
Normal MRI

- Depression – small incidence, esp. in the 1st 6 months of interferon ß therapy
- Benign headache, a common reported side effect of various medications (incl. fingolimod*)



*Patten et al., MSJ 2005 (10.1191/1352458505ms1144oa)

Cystoid Macular Edema – fingolimod



Afshar et al., *JAMA Ophthal* 2013

RCVS

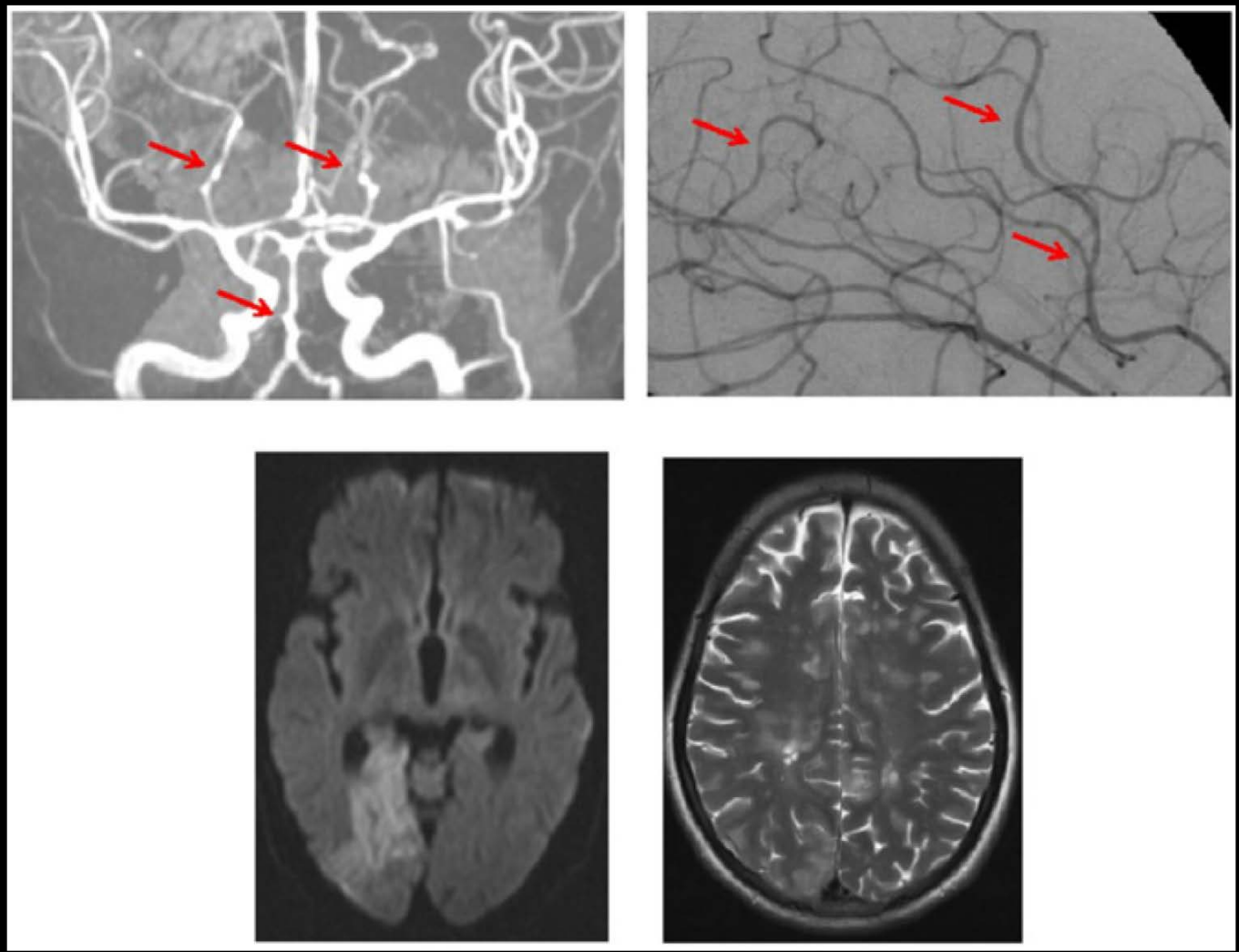
- “thunderclap headache”
- often drug-induced (but also occurs during/immediately after pregnancy)
- 2 cases reported on fingolimod
- multifocal narrowing in Circle of Willis, with post-stenotic dilatation
- no subarachnoid hemorrhage
- vascular findings resolve

Case Report

Reversible cerebral vasoconstriction syndrome associated with fingolimod treatment in relapsing–remitting multiple sclerosis three months after childbirth

Multiple Sclerosis Journal
2015, Vol. 21(11) 1473–1475
DOI: 10.1177/1352458515600249

Markus Kraemer, Ralph Weber, Michèle Herold and Peter Berlit



Tumefactive MS

Tumefactive multiple sclerosis lesions under fingolimod treatment
Femke Visser, Mike P. Wattjes, Petra J.W. Pouwels, et al.
Neurology 2012;79;2000-2003 Published Online before print October 3, 2012

LETTER TO THE EDITOR

CNS Neuroscience & Therapeutics

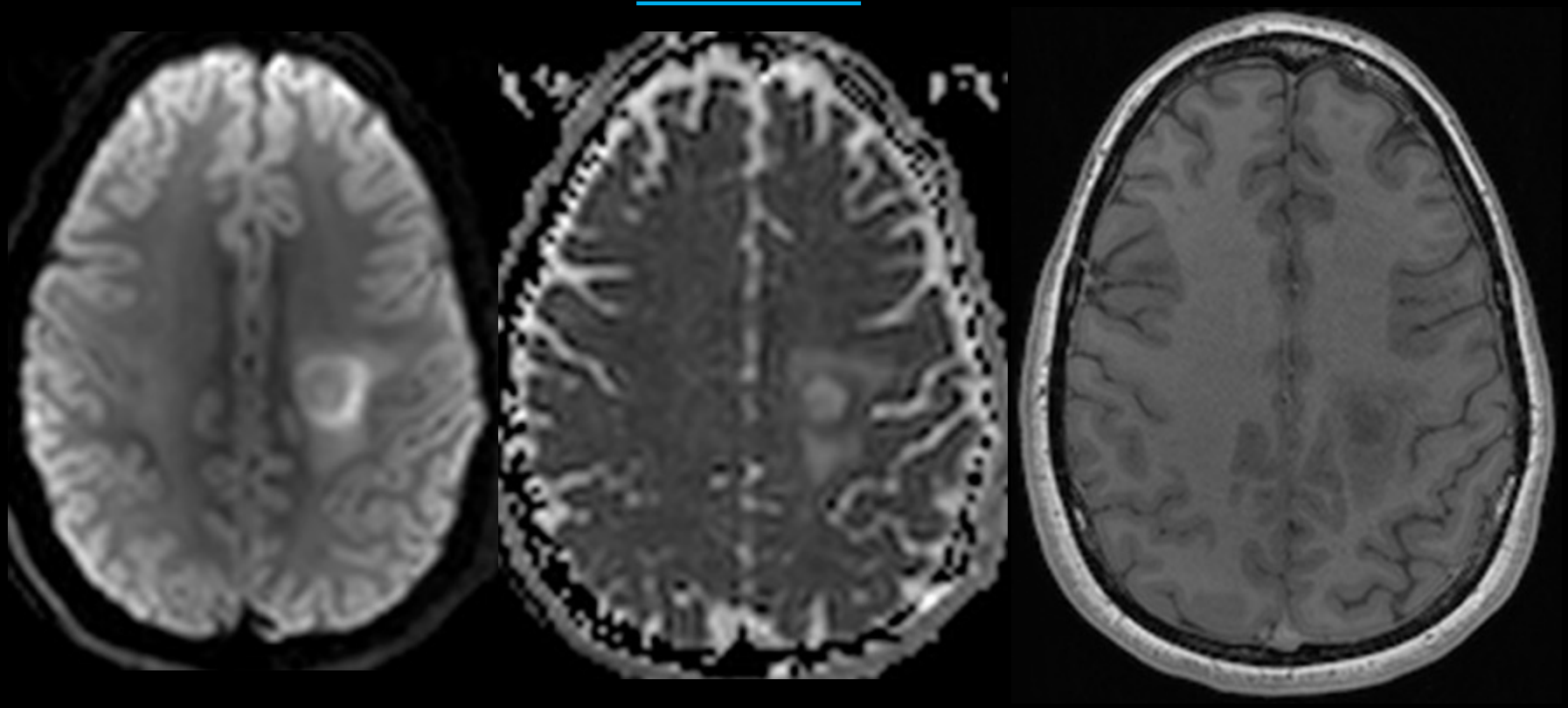
Catastrophic Magnetic Resonance Images in the Central Nervous System of Patients Undergoing Treatment with Fingolimod

Yara Dadalti Fragoso[1] & Henry Koiti Sato[2]

CNS Neuroscience & Therapeutics **22** (2016) 633–635

baseline

1.5 months later

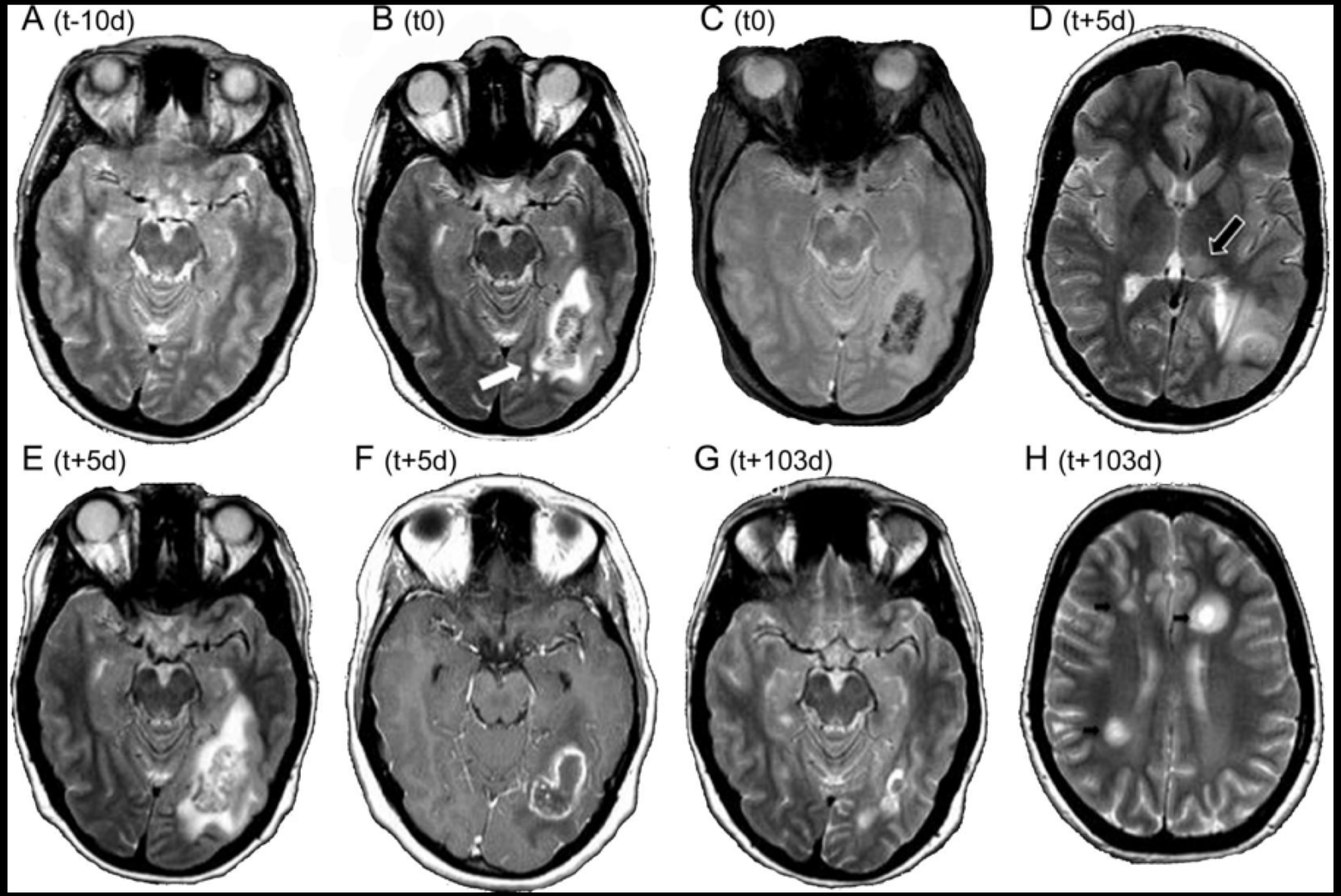


See Schindler et al. ECTRIMS 2017, P1036

HEMORRHAGING FOCAL ENCEPHALITIS UNDER FINGOLIMOD (FTY720) TREATMENT: A CASE REPORT

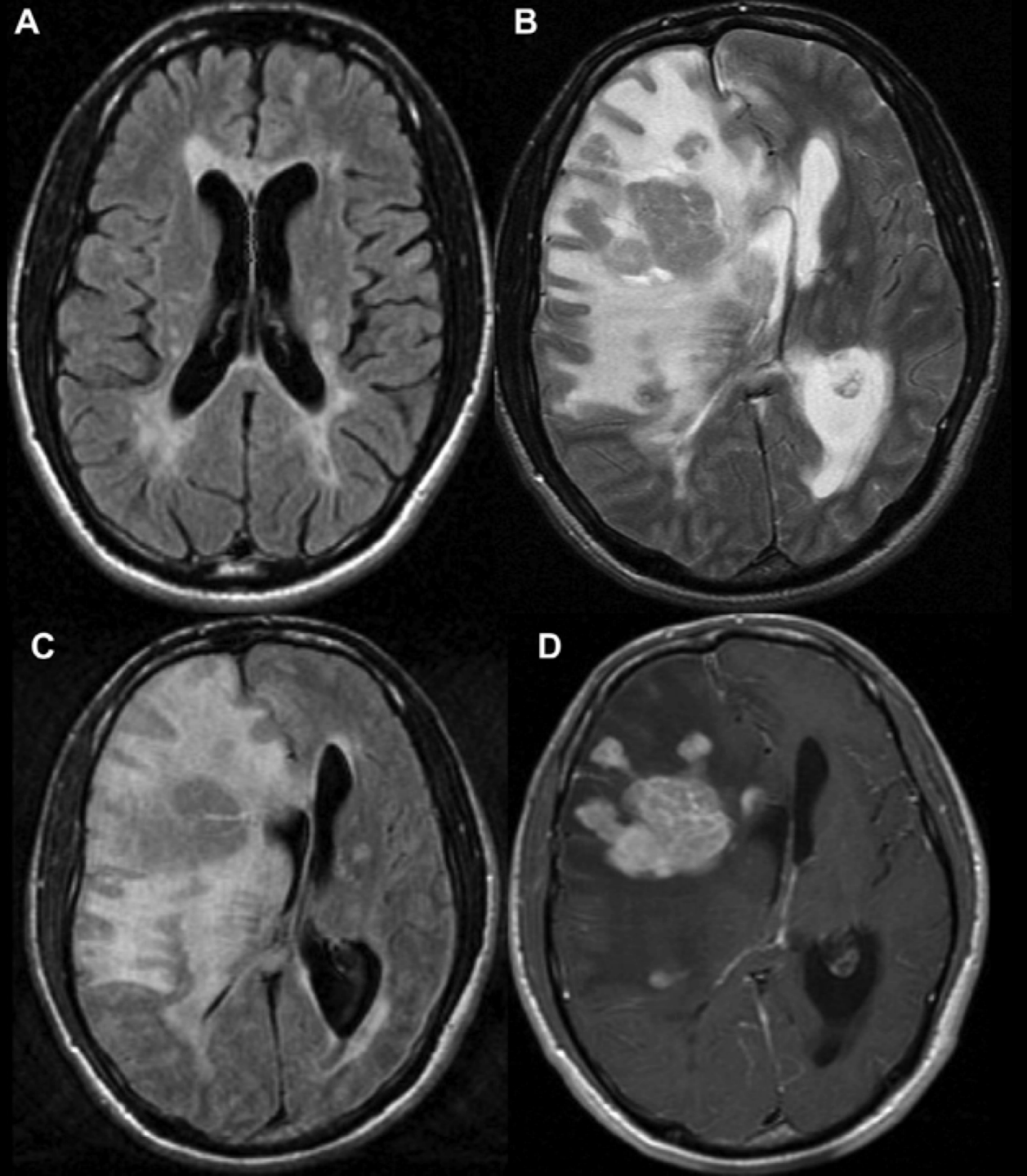
F. Leypoldt, A. Münchau, F. Moeller, et al.

Neurology 2009;72;1022-1024



Primary CNS Lymphoma

- ~8 cases of PCNSL reported on natalizumab therapy since 2009
- cells can show EBV reactivity (inconsistent)
- dense contrast enhancement, but can be peripheral in immunocompromised (has been seen in natalizumab-associated)
- *other characteristics:* T2 isointensity, diffusion restriction



Central nervous system lymphoma associated with natalizumab

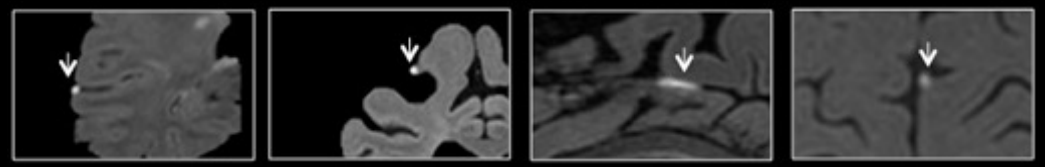
Angelika Na[a], Nick Hall[a], Bhadrakant Kavar[a], John King[b,*]

Case Reports/Journal of Clinical Neuroscience 21 (2014) 1068–1070

Aseptic meningitis

- 1 case reported so far
- leptomeningeal enhancement on post-gad FLAIR 1 day after natalizumab, with headache, fever, photophobia, nausea, & meningismus 3 days later
- recurred after the next infusion
- enhancement resolved

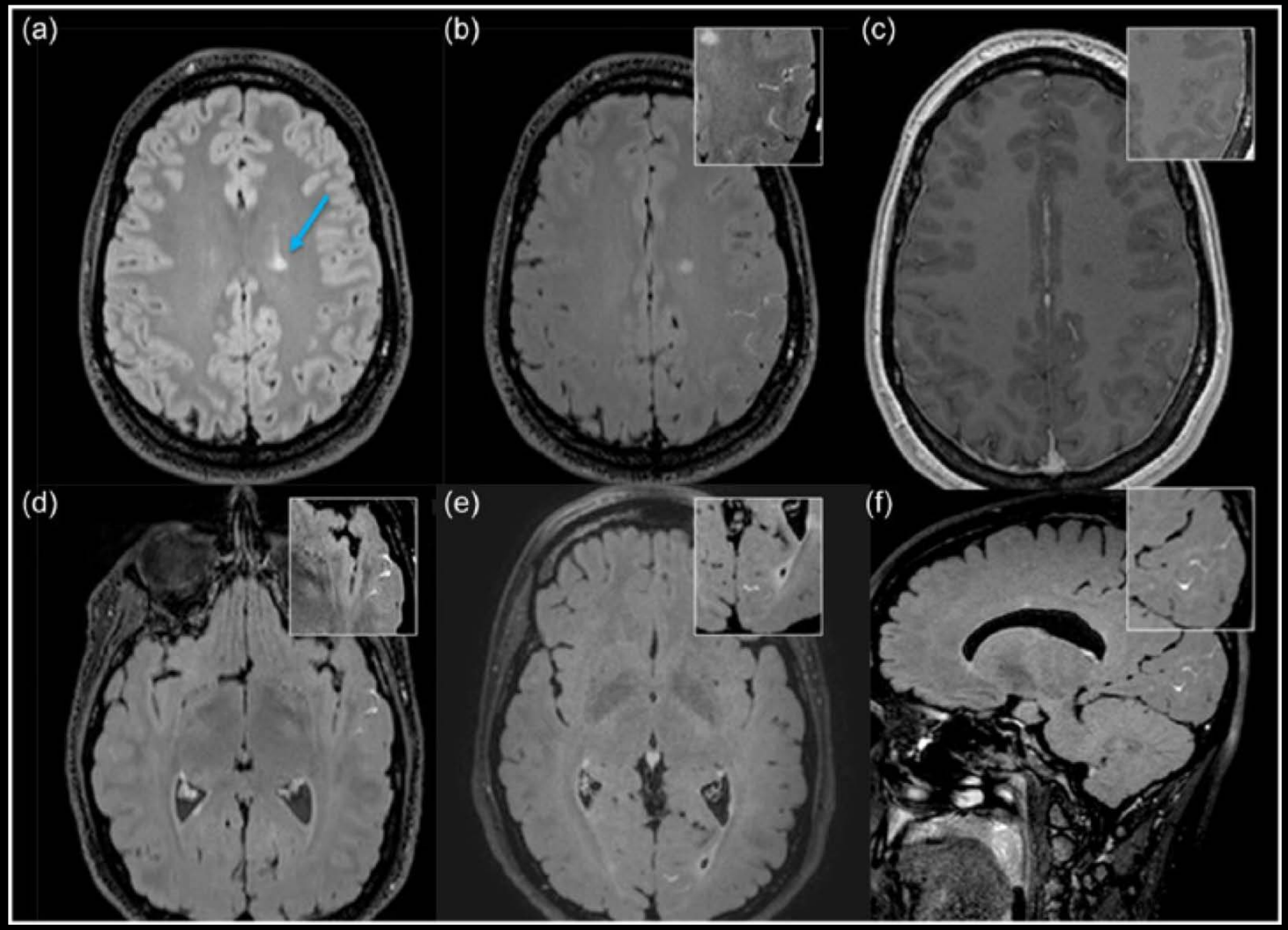
- *different from leptomeningeal enhancement of MS (Absinta, Vuolo et al. 2015)*



Recurrent natalizumab-related aseptic meningitis in a patient with multiple sclerosis

Robert W Foley, Nathan T Tagg, Matthew K Schindler, Kaylan M Fenton, Daniel S Reich, Irene Cortese and Ellen M Mowry

Multiple Sclerosis Journal
2017, Vol. 23(10) 1424–1427
DOI: 10.1177/1352458517702533



OBSERVATION

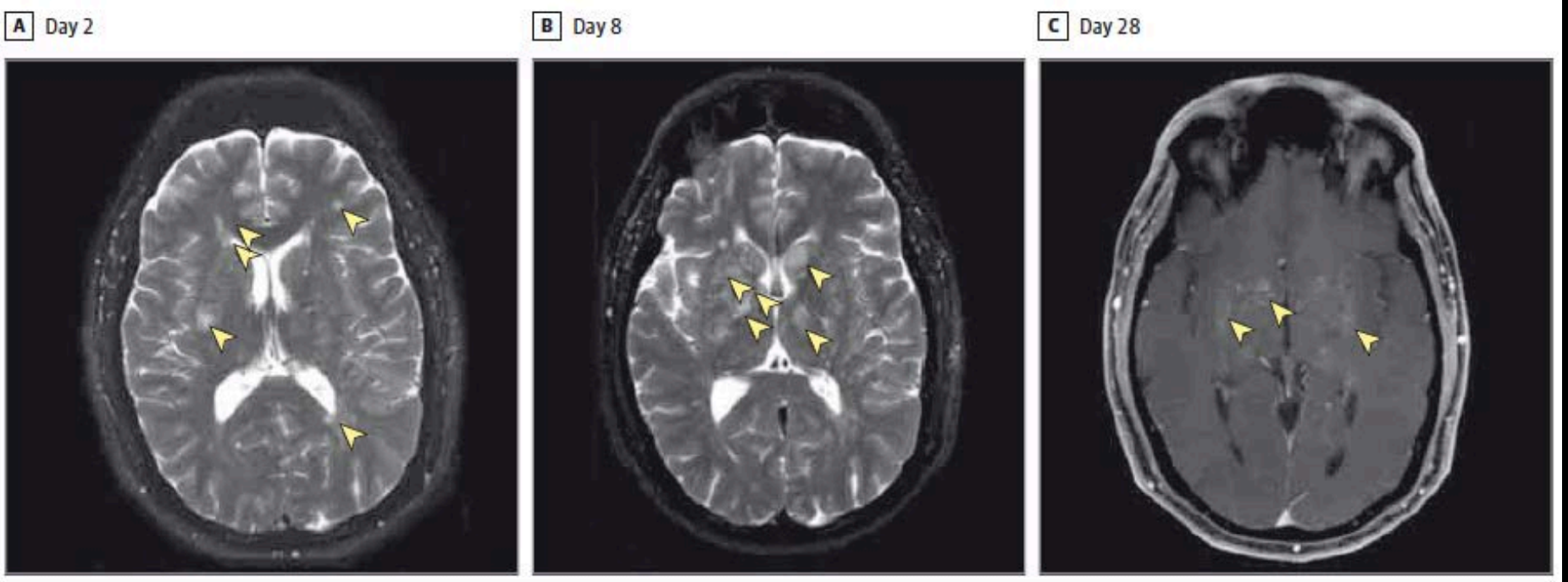
Cryptococcal Meningoencephalitis in a Patient With Multiple Sclerosis Treated With Fingolimod

1204 JAMA Neurology October 2015 Volume 72, Number 10

Lutz Achtnichts, MD
Otilia Obreja, MD, PhD
Anna Conen, MD
Christoph A. Fux, MD
Krassen Nedeltchev, MD

- perivascular space involvement
- hydrocephalus
- parenchymal cryptococcomas
- gelatinous pseudocysts

Figure. Magnetic Resonance Imaging (MRI) Findings on Repeated Examinations



A, On day 2, axial T2-weighted MRI shows multiple nonenhancing supratentorial and infratentorial (not shown) lesions (arrowheads). B, On day 8, new T2-weighted MRI lesions in the basal ganglia, again without gadolinium enhancement (arrowheads). Similar lesions were also identified in the pons and the mesencephalon (not shown). C, On day 28, gadolinium enhancement in the basal ganglia on T1-weighted MRI (arrowheads).

Toxoplasmosis

- T1 dark/T2 bright
- ring or nodular enhancement
- peripheral edema
- lipid/lactate peak on MRS
- can calcify post-treatment

- can looks like MS... but probably no central vein sign

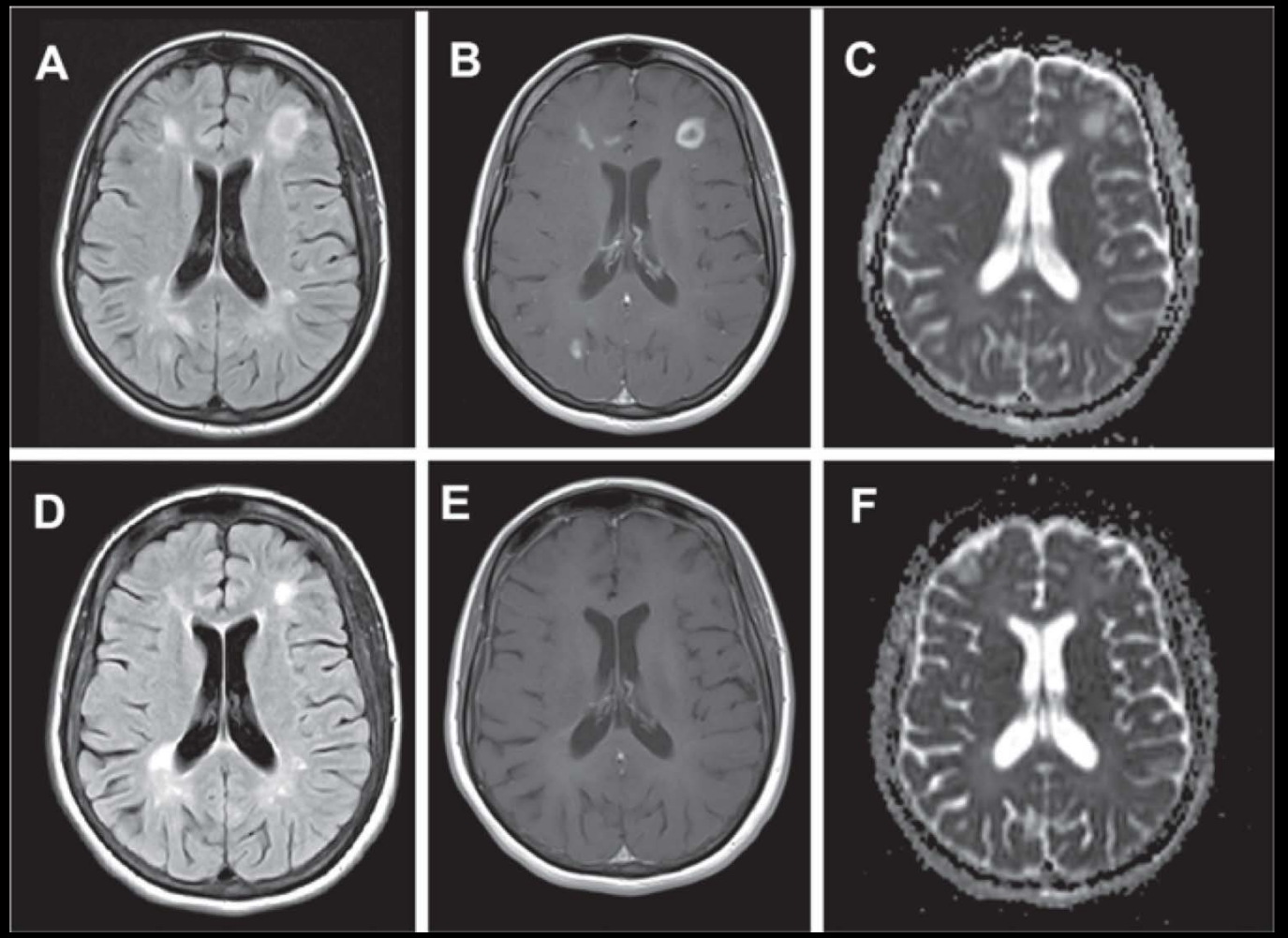
Case report

Cerebral toxoplasmosis in an MS patient receiving Fingolimod

Alejandro Enriquez-Marulanda[a,b], Jaime Valderrama-Chaparro[a,c], Laura Parrado[a,c], Juan Diego Vélez[a,c], Ana Maria Granados[a,b], Jorge Luis Orozco[a,c], Jairo Quiñones[a,c,*]

[a] Fundación Valle del Lili, Cali, Colombia
[b] Clinical Research Centre, Cali, Colombia
[c] Universidad ICESI, Cali, Colombia

Multiple Sclerosis and Related Disorders 18 (2017) 106–108



Question 1

A 50-year-old man with MS, treated with fingolimod, developed seizure and coma. MRI revealed a diffusion-restricting lesion in the medulla. The most likely diagnosis is:

A. Herpes simplex encephalitis
B. Varicella zoster vasculitis
C. Progressive multifocal leukoencephalopathy
D. Reversible cerebral vasoconstriction syndrome

Answer: B

Question 2

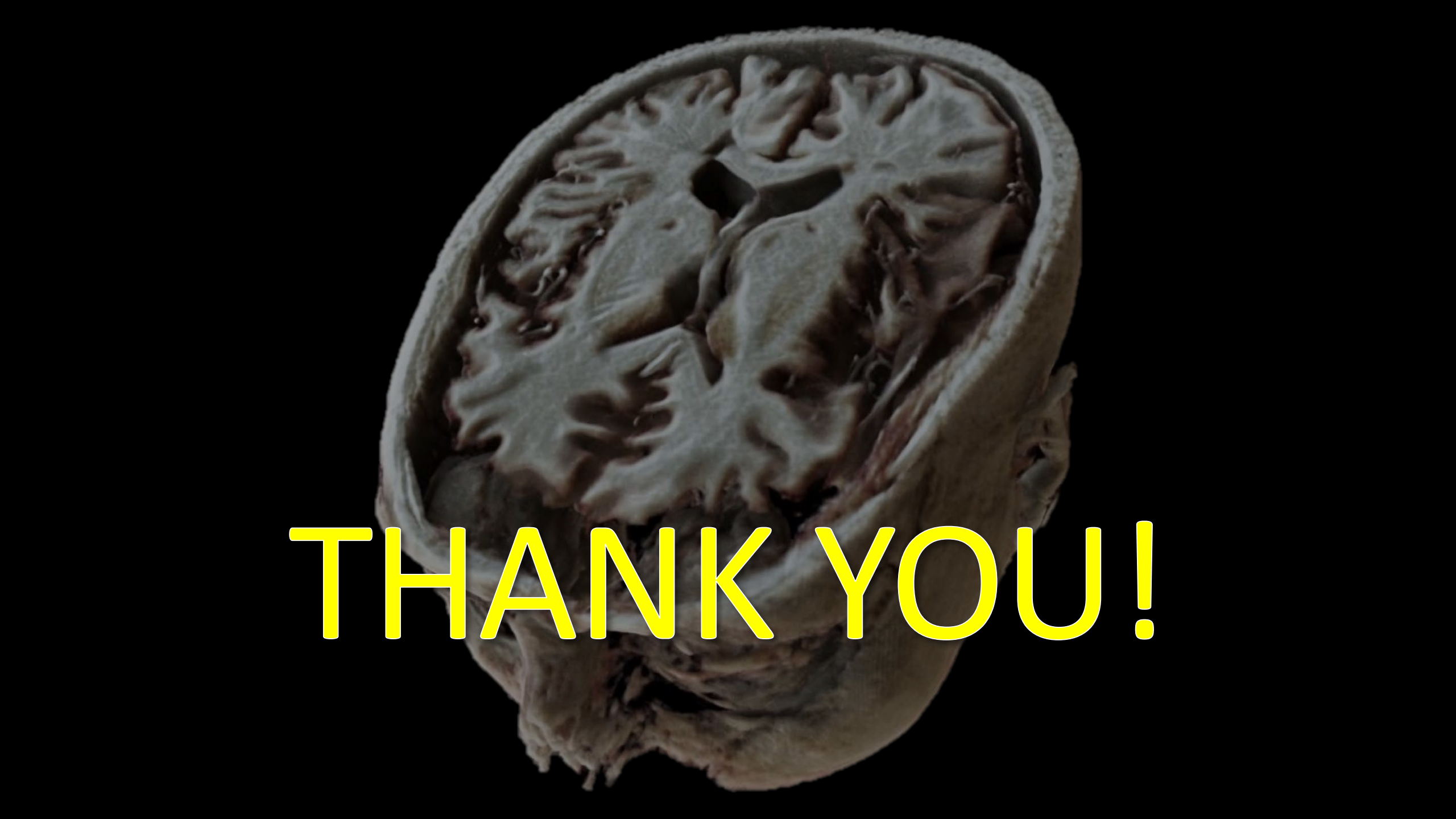
New gadolinium enhancement in a patient with MS and PML may indicate all of the following *except*:

A. PML-induced blood-brain-barrier breakdown
B. Immune reconstitution inflammatory syndrome (IRIS)
C. A new MS lesion
D. A capillary telangiectasia

Answer: D

Summary: Questions to Consider

- Should monitoring be routine or symptom-driven?
- How often to scan?
- Are special imaging sequences useful?
- Should the radiological approach to MS be modified?
- Is a new finding due to MS, MS treatment, or something else?
- How long should pharmacovigilance continue after risky treatment is discontinued?


THANK YOU!