

Monoclonal antibodies – what the diagnostic Neuroradiologist needs to know

Supplement A:

MECHANISMS OF ANTIBODY PASSAGE ACROSS THE BBB:

Generally, only ~ 0.1% of circulating Ab enter the brain and they do so via the following mechanisms:

(i) Adsorptive-mediated endocytosis (AMT) - a mechanism of BBB transport that relies on an electrostatic interaction between a cationic Ab molecule in the circulation and the negatively charged cell membrane at the BBB, which will in turn trigger internalization of the positively charged molecule [1]. Drawback is that cationized molecules can interact with negatively charged cell membranes of peripheral organs thus decreasing their brain uptake [2,3].

(ii) Carrier-mediated transport (CMT) is a mechanism by which small molecules rapidly cross the BBB.

Drawback is that this is a challenging process for Ab transport because these carriers typically transport only small molecules and are highly selective. [2,3]

(iii) Receptor-mediated transcytosis (RMT). This process entails binding of the ligand to the receptor, internalization of the ligand–receptor complex, and exocytosis on the abluminal side of the cell [4]. Drawback of this method is that, when internalized, Abs follow the lysosomal pathway, resulting in their degradation. However, optimizing the affinity of the ligand that is targeting these receptors has proved to be an effective strategy to counter this drawback [5]. Several novel approaches to optimize BBB transgression and uptake of Abs are currently under development [5-9].

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Supplement B:

OTHER IMMUNOSUPPRESSIVE mAbs

Efalizumab

Efalizumab is a humanized therapeutic monoclonal antibody directed against CD11a (expressed on all leucocytes). By binding to CD11a, it inhibits T cell interaction with its cognate endothelial ligand thus inhibiting leucocyte trafficking through the vasculature to areas of tissue inflammation. It is used for the treatment of adult patients with chronic moderate to severe plaque psoriasis [1] and multiple sclerosis. The incidence of PML associated with Efalizumab was deemed to be unacceptably high, and hence led to its withdrawal from the market in 2009. The estimated risk of PML with Efalizumab in 2009 was 1 : 400, in contrast to the 1 :1000 risk of PML associated with NTZ at this time [2-3].

Rituximab

Rituximab (RIX): is an anti-CD20 monoclonal antibody therapy that induces depletion of mature B cells and pre B cells responsible for production of autoantibodies [5].

It is used as an anti cancer drug_ in follicular lymphoma, diffuse large B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukemia, but also in autoimmune conditions such as severe rheumatoid arthritis, Wegener granulomatosis, and microscopic polyangiitis. The incidence of rituximab associated PML has been quoted at 1 of 30,000 cases in 1 review [4]. It is likely that the risk of developing PML depends on the patient's underlying diagnosis and may be higher in those with lymphoproliferative disorders.

Brentuximab–vedotin

Brentuximab–vedotin (BV): is an antibody drug conjugate composed of a chimeric immunoglobulin (Ig)G mAb directed against CD30 conjugated to a cytotoxic agent, leading to induction of apoptosis.

CD30 is a member of the TNF receptor (TNFR) superfamily and is expressed on activated T and B lymphocytes. It is used for the treatment of recurrent or refractory anaplastic large cell lymphoma and Hodgkin's lymphoma.

The risk of PML has been flagged up recently in the FDA's adverse event reporting database [6]. Although rare with 1.47% [7], a noteworthy feature of BV-induced PML is the rapidity of onset of symptoms within weeks of treatment in contrast to a median of 63 weeks after rituximab, and 26 months after NTZ [7].

Alemtuzumab

Alemtuzumab (Alem): A potent humanized monoclonal antibody targeted at activated lymphocytes and monocytes, Alem induces pronounced sustained immunosuppression characterized by global lymphopenia. [8] It is used in resistant CLL and for RRMS [8].

Given its pronounced immunosuppressive effects on T cells, it is surprising that PML has not been reported more frequently. Currently, reports of PML have been confined to case reports [9-11], however not in patients with MS [12]. One possible explanation for the lack of PML to date in MS patients may be the use of Alemtuzumab in a less immunosuppressed cohort in contrast to CLL patients, who are likely to have been pretreated with other immunotherapeutic regimens.

Eculizumab.

Eculizumab is a humanized monoclonal antibody targeted against complement C5 thus inhibiting deployment of the membrane attack complex (MAC) that is the final effector pathway of complement activation [13].

It is approved for the treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) [14], but its use is also widely accepted for patients with severe secondary thrombotic microangiopathy (TMA) [15, 16], refractory generalized myasthenia gravis [17] and Neuromyelitis Optica Spectrum Disorder (NMOSD) [18].

PML in association with Eculizumab is exceedingly rare with a single case reported in the literature [19].

Supplemental Table

Monoclonal Antibody Therapies and their Use in Neurologic Diseases

Drug	Target	Mechanism of Action	Condition used	Side Effects
Alemtuzumab (Campath)	CD52	Depletes T and B cells via an unknown mechanism	Multiple sclerosis	<ul style="list-style-type: none"> systemic autoimmune diseases (thyrotoxicosis, immune thrombocytopenic purpura and Goodpasture's syndrome) PML
Efalizumab	CD11a	inhibiting leucocyte trafficking to areas of inflammation.	chronic moderate to severe plaque psoriasis	<ul style="list-style-type: none"> PML
Eculizumab	Complement-C5	Inhibits MAC formation	PNH, aHUS, TMA, MG, and NMOSD	PML*
Rituximab	CD20	Induces cell lysis and reduces the total B-cell count	NMO, Multiple Sclerosis, immune neuropathies, dermatomyositis, MMN	PML
Brentuximab-vedotin	CD30 receptor	apoptosis of CD30-positive cells	Recurrent or Refractory Anaplastic Large Cell Lymphoma and Hodgkin Lymphoma.	PML PML-IRIS

Abbreviations:

IL-2, interleukin 2

MMN, multifocal motor neuropathy

NMO, neuromyelitis optica

TNF, tumor necrosis factor

MNM: mononeuritis multiplex

GB: Guillain-Barré syndrome

*Equivocal causality relationship but considered.

Supplement D

References:

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Supplement C:

Clinical Management of ARIA

Clinical Management is based on patient symptomatology, and imaging criteria [1] with the radiologist playing a major role in the evaluation of patients treated with these new drugs as outlined by the white paper of Cogswell: For asymptomatic patients, dosing was continued with mild ARIA-E and/or mild ARIA-H, while dosing was suspended with moderate ARIA-E and/or moderate ARIA-H. Once dosing was suspended due to imaging findings, serial imaging was performed monthly, and dosing was resumed following the resolution of ARIA-E and stabilization of ARIA-H. For symptomatic patients, dosing resumed only after both the resolution of clinical symptoms and the resolution of ARIA-E and stabilization of ARIA-H. Dosing was permanently discontinued with severe ARIA-H (≥ 10 treatment-emergent microhemorrhages or > 2 areas of treatment-emergent superficial siderosis) or a macrohemorrhage (> 10 mm in diameter).

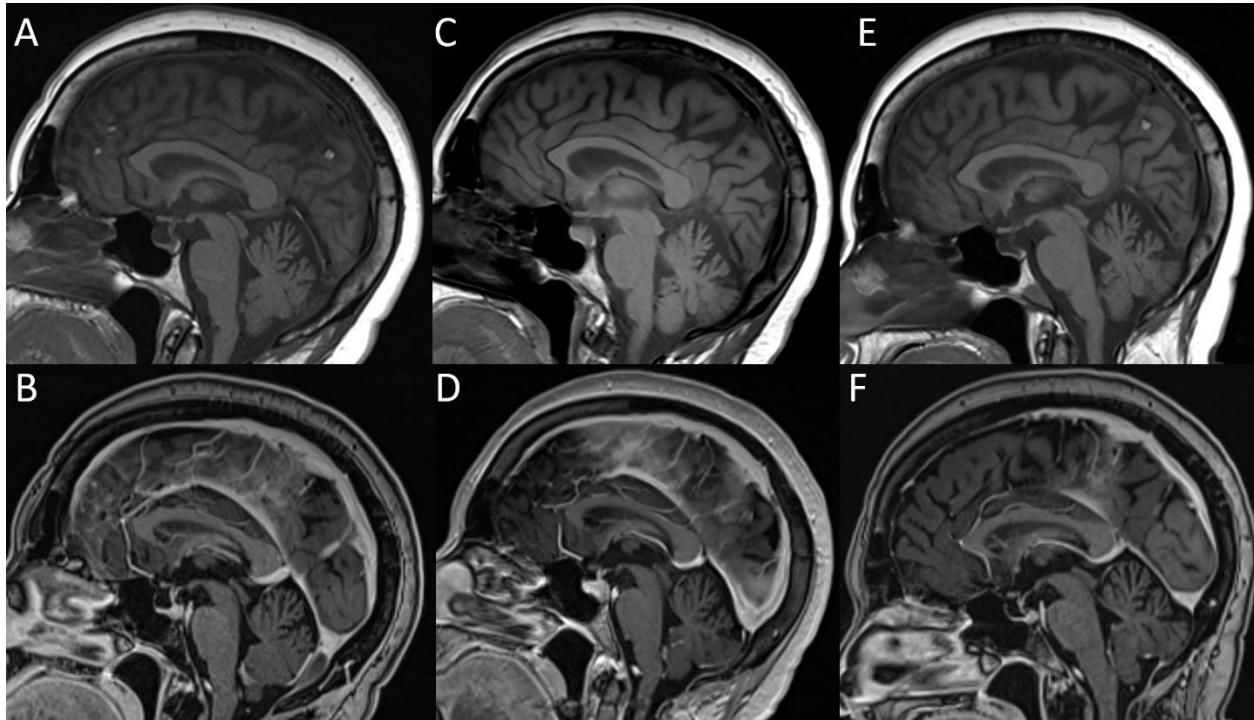
As clinical management relies on imaging, the Radiologist plays a major role in the evaluation of patients treated with mAbs for AD, detailed description and accurate assessment with standardized imaging acquisition parameters and reporting within an institution or practice and ideally across institutions are needed to obtain accurate longitudinal assessment. To promote such efforts, recommendations for an imaging protocol are provided in a white paper by Cogswell et al [1] and a recommended reporting template is posted on the American Society of Neuroradiology website at <https://www.asnr.org/alzheimers-webinar-series/>. Both the imaging protocol, and the recommended reporting template will be updated as experience and knowledge evolve.

Reference:

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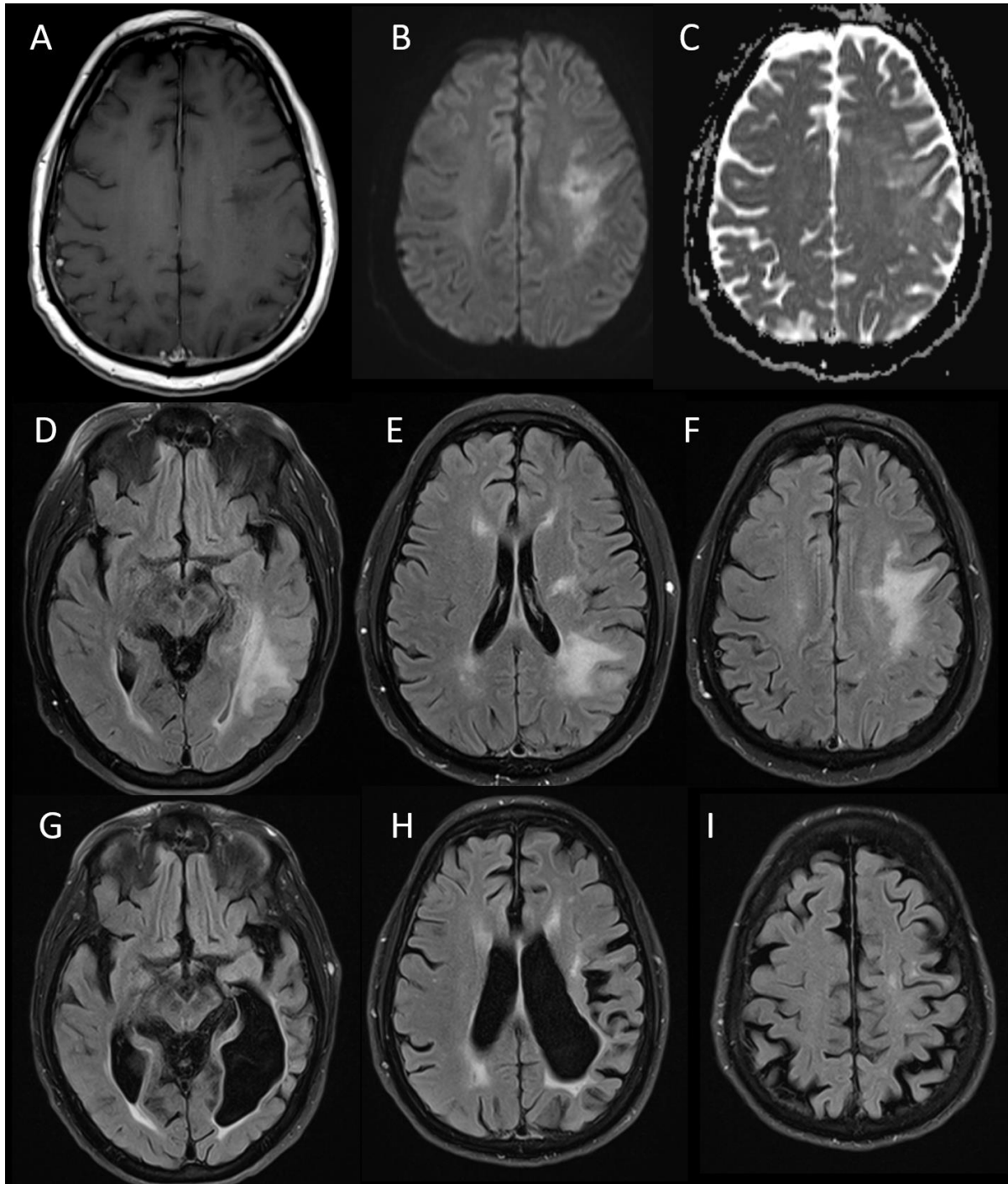
Supplement D:

Supplemental FIGURES



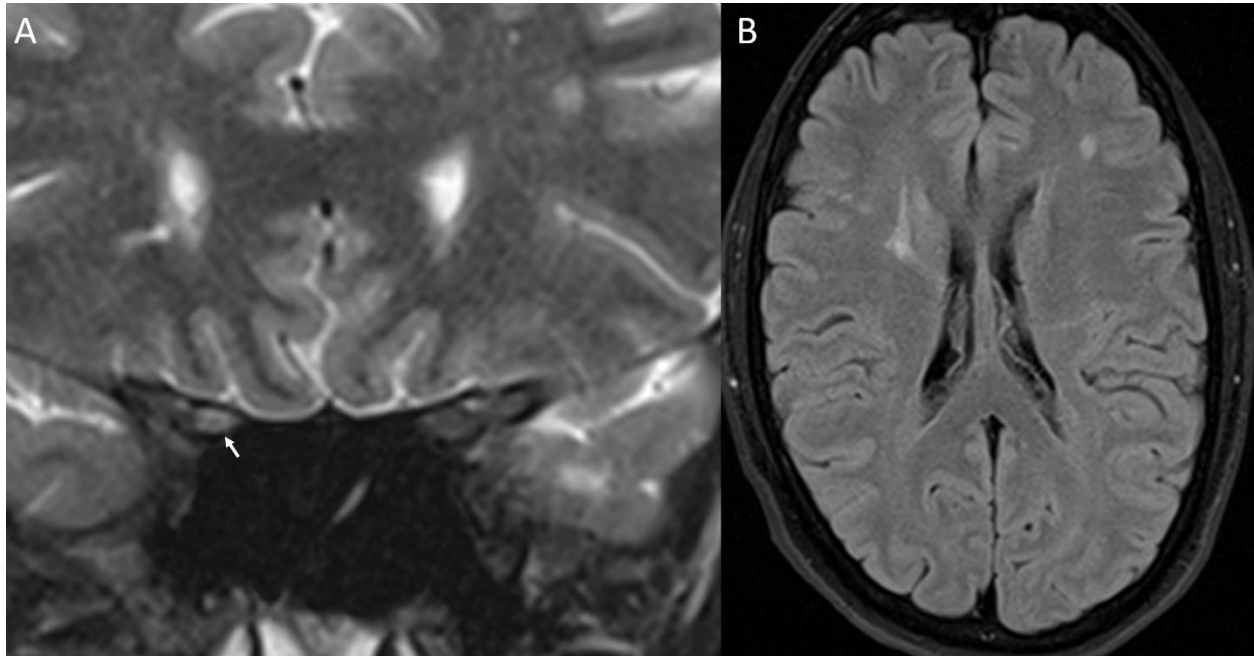
Supplemental Figure A

Hypophysitis induced by anti-CTLA-4 mAbs. Time course of Ipilimumab induced hypophysitis in a 71 old female with a metastatic melanoma. Frames A and B demonstrate unenhanced (A) and enhanced (B) sagittal T1 weighted scans prior to initiation of treatment, Frames C and D were obtained after 5 months of treatment and Frames E and F 8 months after cessation of Ipilimumab treatment. Significant interval growth is seen that is symmetrical and leads to homogeneous enhancement of the gland and regresses completely after cessation of treatment thus ruling out the major differential diagnosis, i.e. pituitary metastatic deposit



Supplemental Figure B

Natalizumab induced PML - chronic brain tissue loss. PML in a 55 year old male patient treated with Natalizumab for ankylosing spondylitis. Frame A: T1 post contrast, Frame B DWI and Frame C (ADC) map; Frames D-F T2-weighted Flair scans at various locations at baseline, Frames G-I follow-up MR after 7 years at similar locations with Flair weighted scans demonstrate multiple non-enhancing asymmetrical and subcortical white matter lesions that demonstrate mild DWI hypersignal but no significant restriction and that lead over time to significant brain atrophy in the affected regions.



Supplemental Figure C

Adalimumab induced optic neuritis and demyelinating lesions in a 47 year old treated for psoriatic arthritis. Coronal T2 weighted scans demonstrate abnormal high signal in the right optic nerve (arrow in A) in keeping with optic neuritis. T2 weighted FLAIR scans demonstrate a few demyelinating white matter lesions in the centrum semiovale.