The Effects of Toxins and Therapies on the CNS: Neuropathological aspects

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Disclosures

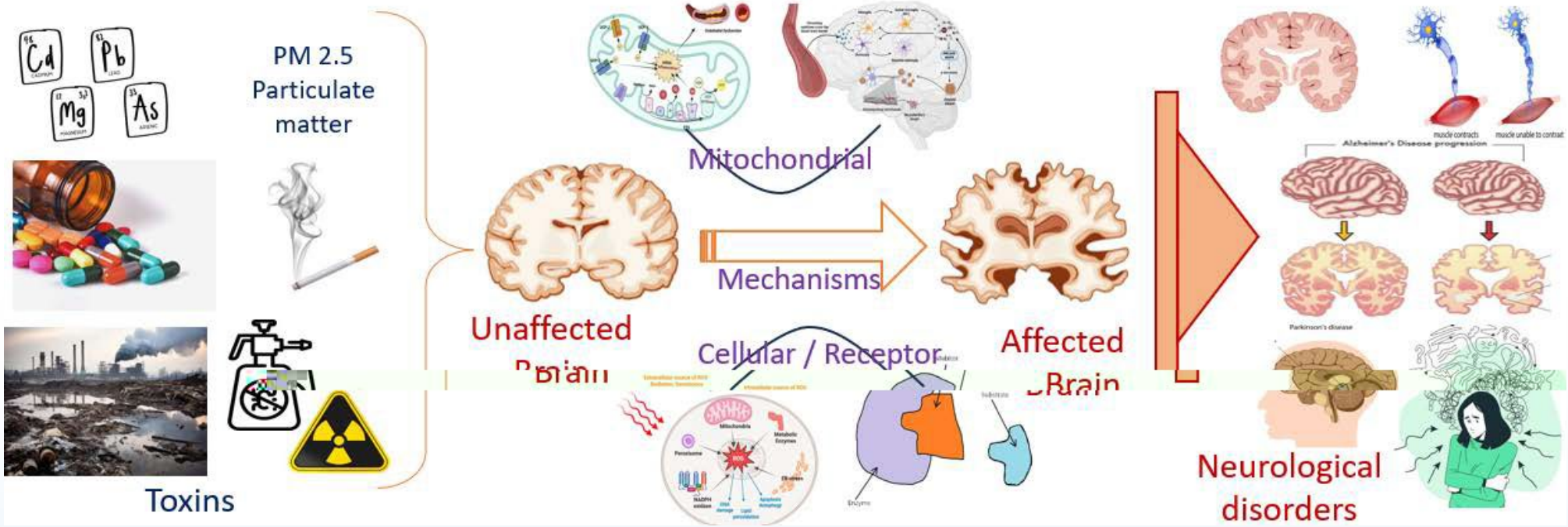
- I have no relevant financial relationships to disclose

Learning Objectives

1. Analyze the mechanisms of neurotoxicity associated with various environmental and therapeutic agents.
2. Recognize the spectrum of neuropathological patterns associated with toxic and therapy-related CNS injury in gross and microscopic specimens.
3. Describe the major neuropathological changes induced by certain neurotoxins.

Outline

- Mechanisms of neurotoxicity
- Effects of “common” neurotoxic agents
- Effects of therapies



MECHANISMS OF NEUROTOXICITY

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Gouri H, Bhalla G. Neurotoxic Chemistry: Unraveling the chemical mechanisms connecting environmental toxin exposure to neurological disorders J. Integr. Sci. Technol.2025, 13(3),1064

Exogenous toxins

- Gases
- Liquids
- Solids

- Natural
- Synthetic

- Industrial and environmental toxins

- Recreational substances

- Pharmaceutical products
  - Non-antineoplastic
  - Antineoplastic
  - Immunomodulators
  - Cellular products

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Variables that determine neurotoxic effects

- Concentration (air pollution vs a spill)
- Duration of exposure
  - Acute
  - Subacute
  - Chronic
- Specific chemical compound (organic vs inorganic lead salts)
- Combination of agents (multiple substances frequently act in synergy)
- Mechanism of exposure (ingestion, inhalation, injection, skin absorption)
- Prolonged survival or recovery after acute exposure impacts neuropathologic change

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Mechanisms	Pathophysiology	Examples
Direct cytotoxicity	Interference with energy metabolism, protein synthesis, membrane integrity	- **Carbon monoxide, Cyanide:** Inhibit mitochondrial cytochrome c oxidase Complex IV. - **Methylmercury:** Accumulates in neurons, disrupting mitochondrial function.
Oxidative stress	Increase in reactive oxygen species (ROS) leads to lipid peroxidation, DNA damage, cell death	- **Paraquat:** Herbicide that induces oxidative stress in dopaminergic neurons. - **Alcohol:** Chronic exposure leads to ROS production and neurodegeneration.
Excitotoxicity	Activation of neurotransmitter receptors	- **Organophosphates:** High levels can cause excitotoxic cell death through glutamatergic receptors - **Cocaine:** Can enhance glutamate release and cause excitotoxic effects.
Disruption of cellular signaling	Pathways involved in cellular survival, growth, synaptic function	- **Antineoplastic drugs (e.g., cisplatin):** Disrupts signaling pathways involved in cell survival. - **Heavy metals:** Can affect calcium signaling pathways in neurons.
Demyelination	Oligodendrocyte/myelin sheath injury	- **Solvents (e.g., toluene):** Can cause myelin damage and lead to central nervous system symptoms. - **Certain chemotherapeutic agents (e.g., methotrexate):** Associated with leukoencephalopathy
Neuroinflammation	T-cell and microglial activation	**- Immune checkpoint inhibitors:** Can induce neuronal injury through cytotoxic T-cell effect

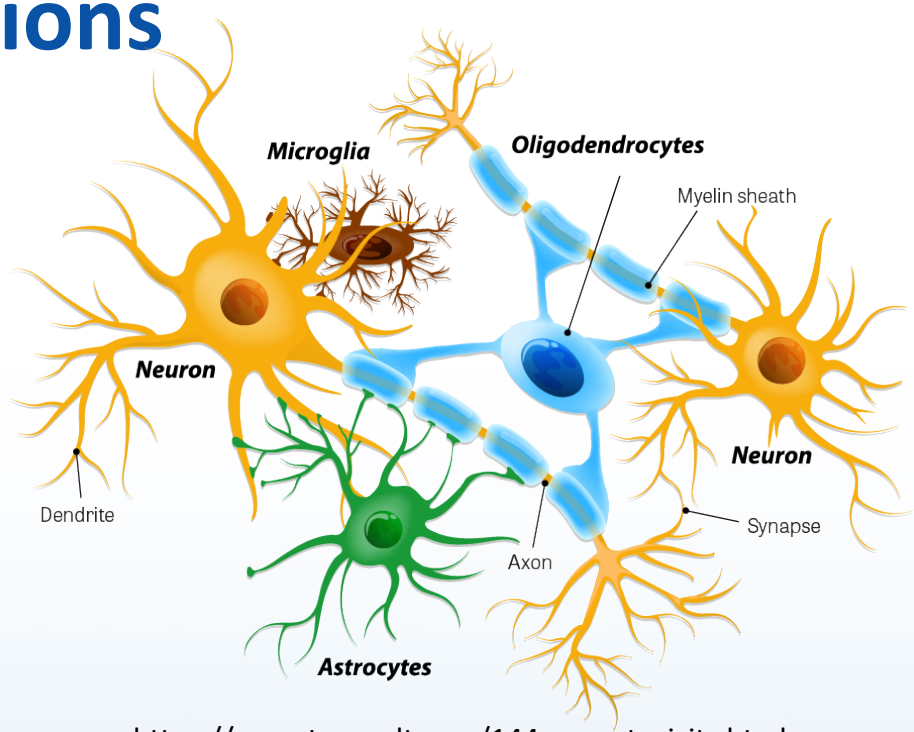
General neuropathologic considerations

Damage can be specific to certain cell type or structure

Damage can be specific to anatomic locations

Acute intoxication commonly manifests as diffuse cerebral edema

Many toxins primarily affect the PNS (not covered)



https://www.toxmsdt.com/144-neurotoxicity.html

CAUSES OF BILATERAL BASAL GANGLIA NECROSIS

Toxic or hypoxic injury

- Carbon monoxide.
- Cyanide.
- Methanol.
- Marchiafava–Bignami disease (usually associated with chronic alcoholism).
- Heroin and other causes of global cerebral hypoxia.

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INDUSTRIAL AND ENVIRONMENTAL AGENTS

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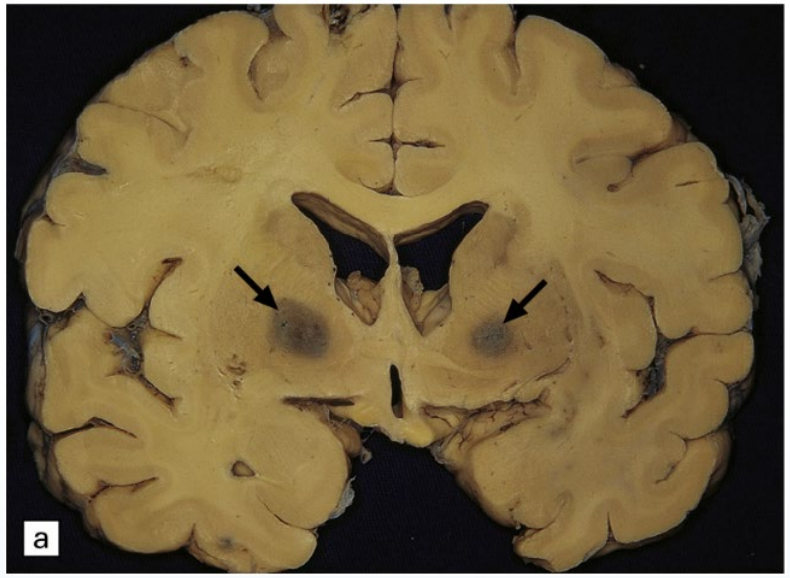
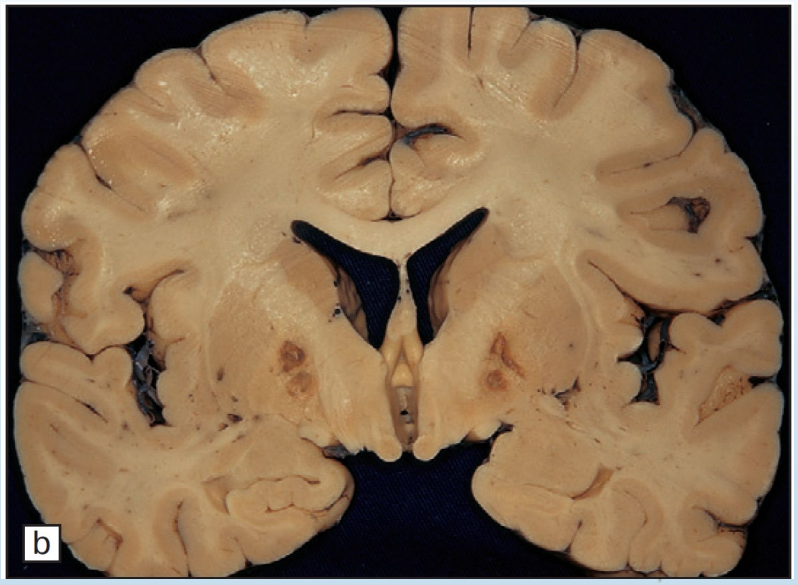
Gases

- **Carbon monoxide**
  - Most common known neurotoxic gas (estimated 450 accidental deaths annually in the US)
  - Prevents binding of O_2 to Hb, increased metabolic demand leads to mitochondrial injury
  - Bilateral injury to globus pallidus is characteristic
  - White matter and other gray matter regions can be involved
  - Cherry red discoloration initially (hours)

- Cyanide:
  - Binds to COX preventing oxidative phosphorylation
  - Inhalation can cause death in minutes





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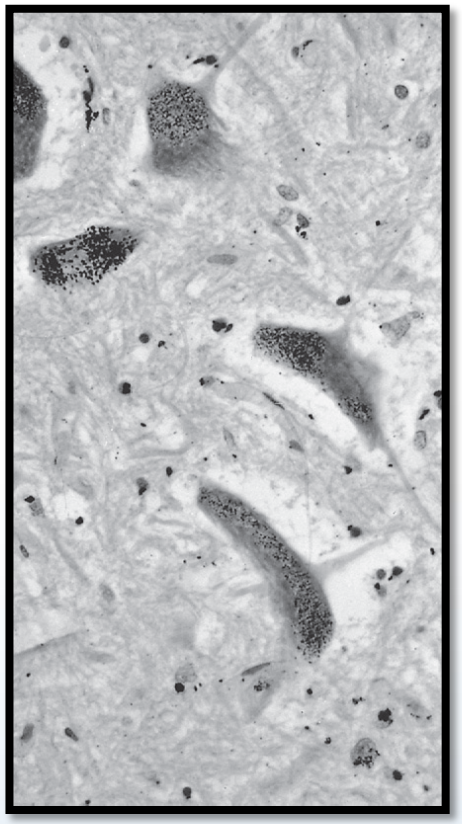
Heavy metals

Dr. Kelly Mrachek during the live session on 8/27 shared:
Aluminum can be detected in tissue using the Morin stain under IF, I've used it for diagnosing aluminum containing macrophages in Macrophagic Myofasciitis (MMF) PMID: 28340105



- Aluminum:
  - Direct neuronal injury
  - Dialysis encephalopathy syndrome: argyrophilic deposits
- Arsenic: acute hemorrhagic leukoencephalopathy
- Lead: cerebral edema with vascular injury, necrosis
- Mercury: small neuron injury (cerebellar granule cells, primary nonmotor cortex), intralysosomal mercury in neurons and glial cells in long-term survivors

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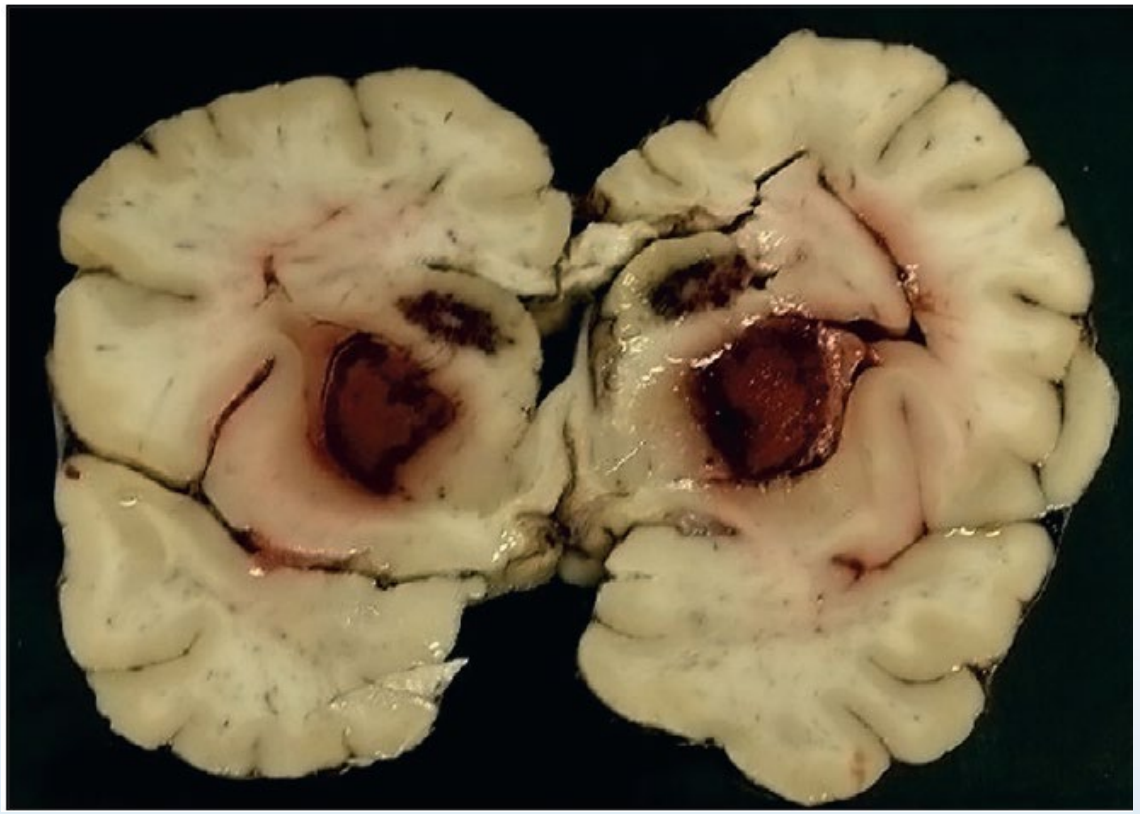
Industrial chemical toxins



- **Methanol**: global hypoxic injury, bilateral hemorrhagic necrosis of the putamen
- Ethylene glycol: vascular injury with birefringent calcium oxalate crystals
- Toluene: cerebellar atrophy with chronic exposure (glue sniffing)

Dr. Marc del Bigio during the live session on 8/27 shared:
Re: Toluene – I have seen >100 autopsy cases of persons who inhale toluene (usually paint thinner solvent) for intoxication. The most common pathology is patchy demyelination with perivascular macrophages that contain birefringent crystalline inclusions (see Al Hajri 2010 Acta Neuropathologica 119:435-445).

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Case 1

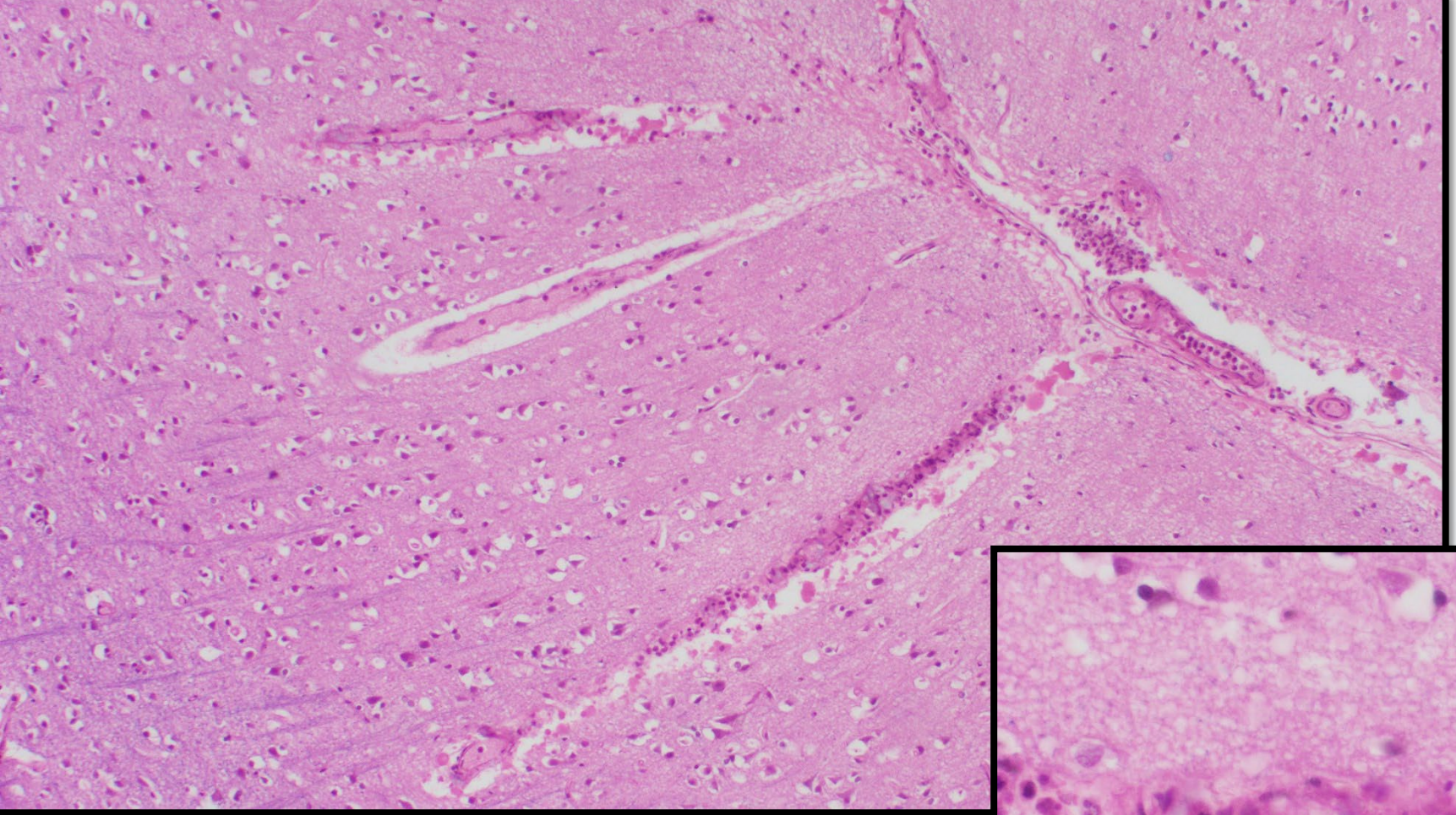
A 22-year-old man was a frequent user of stimulants.

Presented with vomiting, then became incoherent and belligerent, followed by stupor, somnolence and seizures.

He admitted to having ingested “something”, and the police found a half-empty can of antifreeze in the patient’s home

Testing revealed severe metabolic acidosis, which proved resistant to treatment and the patient died.

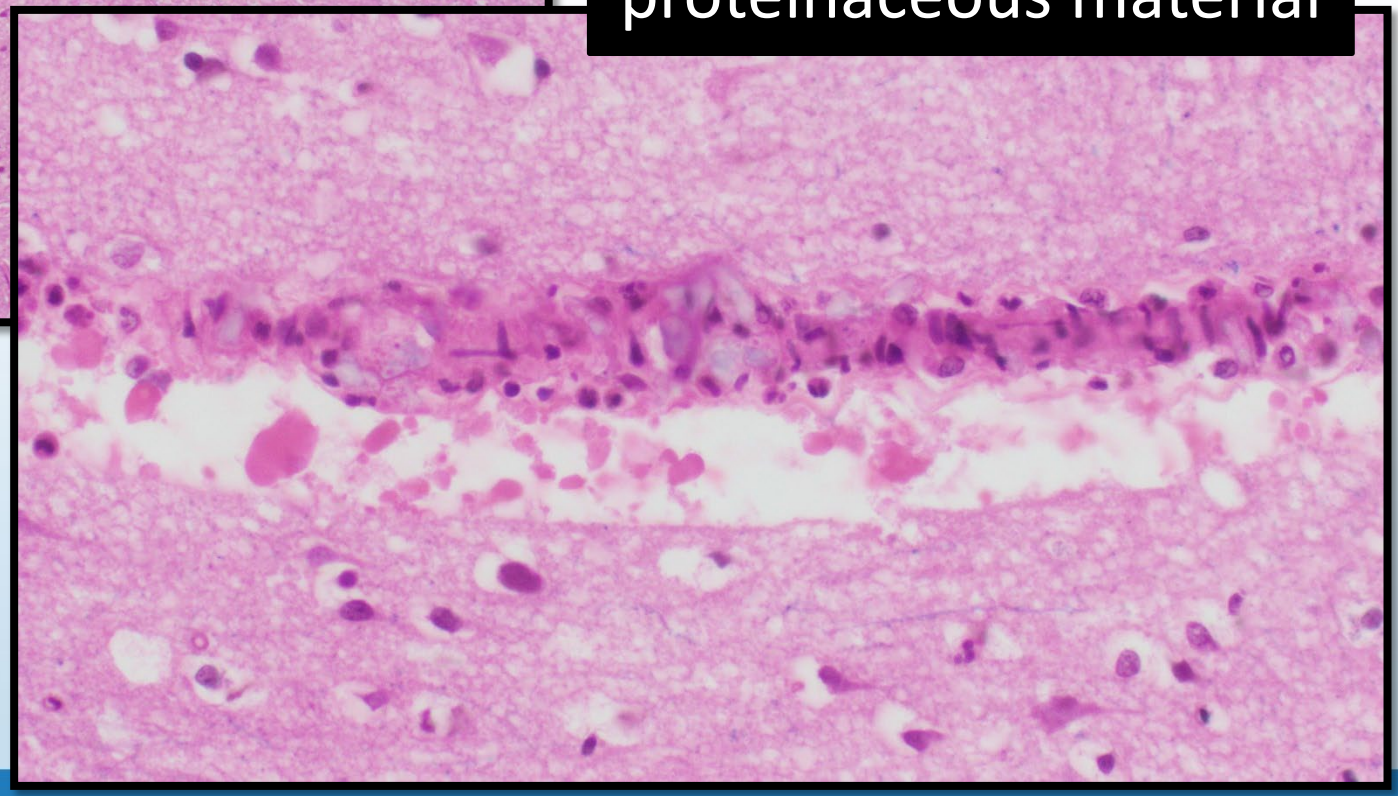
Levinsky, NG, Robert, NJ. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 38-1979. (1979). *The New England journal of medicine*, *301*(12), 650–657.



1610 g brain weight

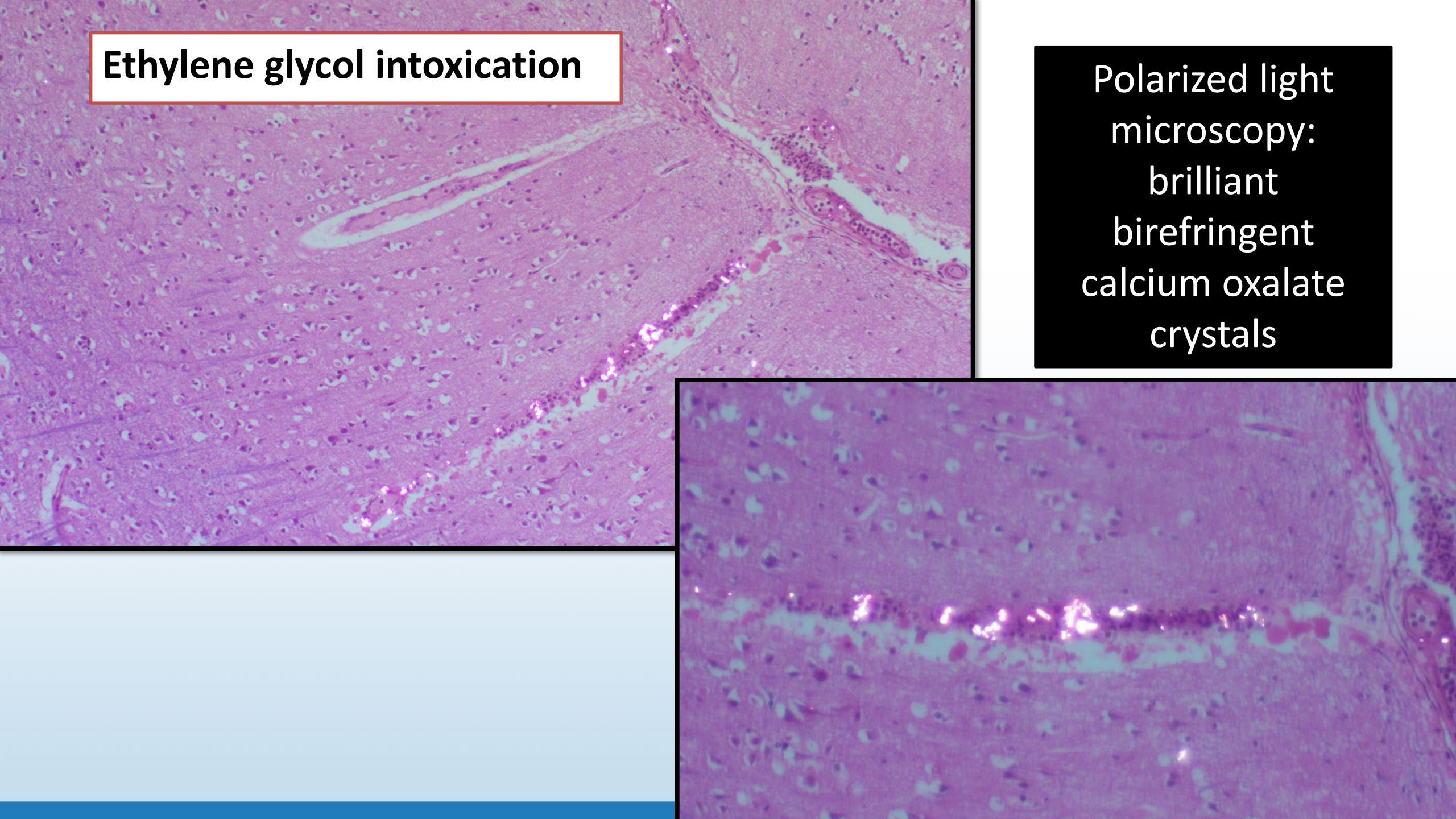
Pericellular edema and neuronal injury

Perivascular proteinaceous material



Ethylene glycol intoxication

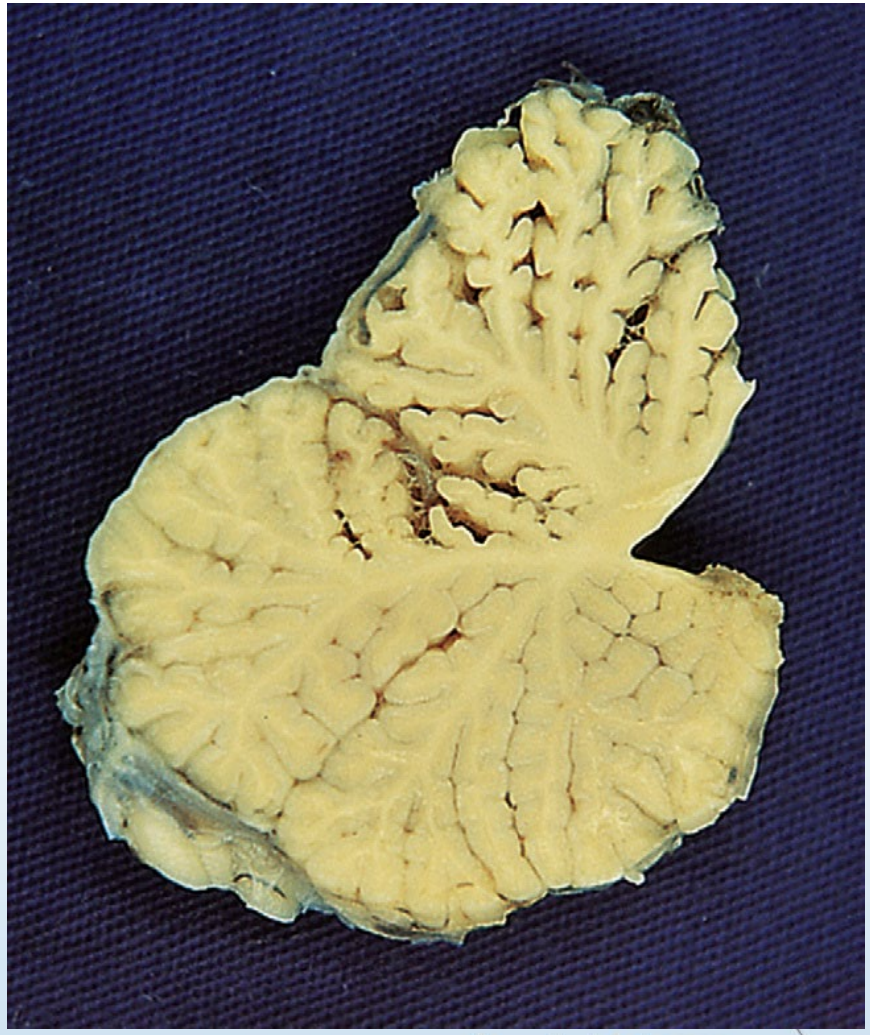
Polarized light microscopy: brilliant birefringent calcium oxalate crystals



RECREATIONAL AGENTS

Ethanol - Alcohol-related brain damage

- Primary injury vs secondary effects of malnutrition or liver disease (distinction may be challenging)
- Diffuse atrophy is the main finding
- Characteristic features
  - Superior vermian atrophy
  - Loss of Purkinje cells
  - Crests of folia more involved than depths



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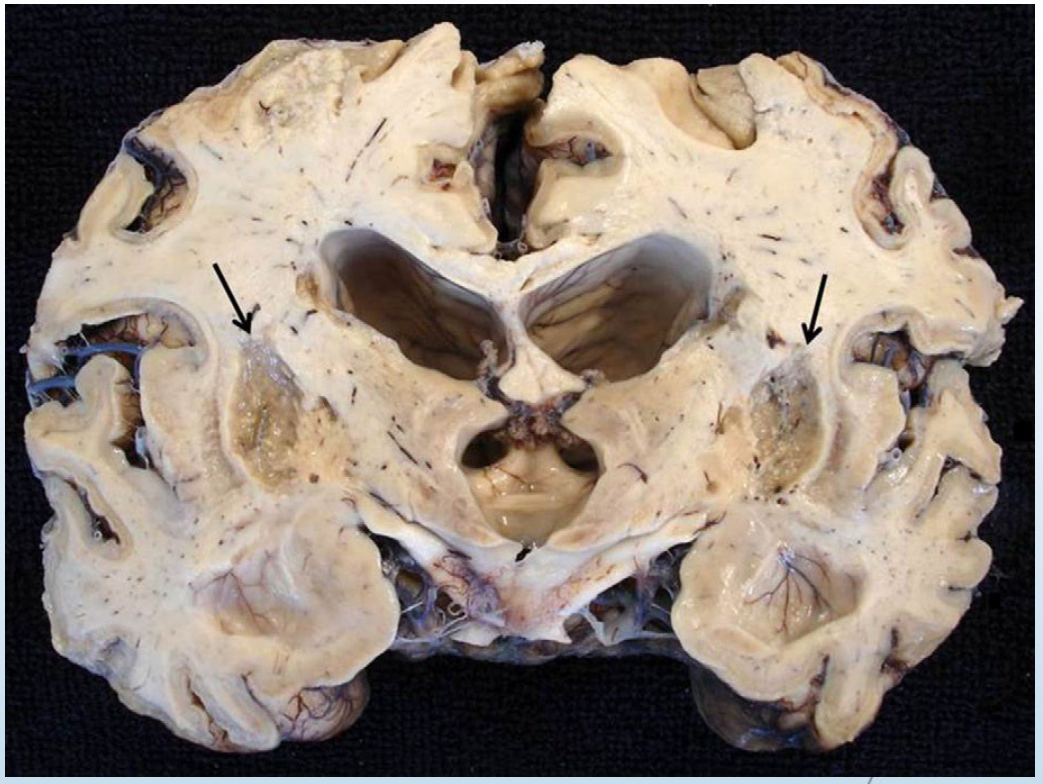
Opioids

- Leading cause of death by substance use (heroin, fentanyl)
- Main mechanism is central respiratory depression

- Oral, injection, inhalation
- Delayed death:

  hypoxic-ischemic (leuko)encephalopathy

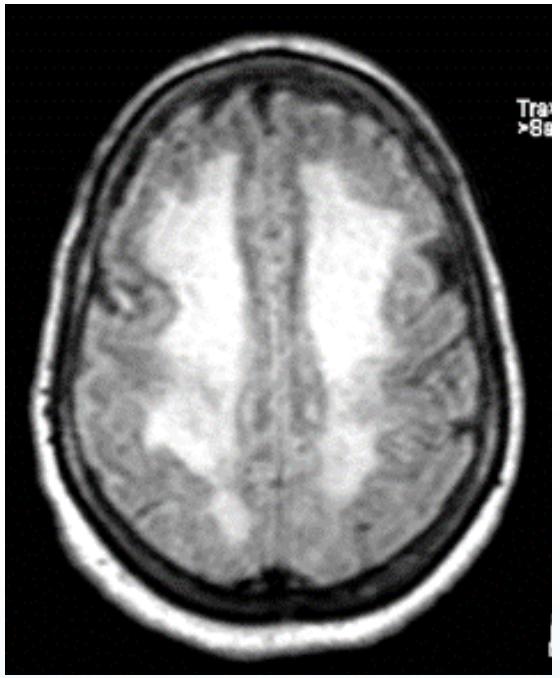


Weis S, Büttner A, Chapter 14 - Neurotoxicology and drug-related disorders. In Kovacs G, Alafuzoff I (eds) Handbook of Clinical Neurology, Elsevier, Volume 145, 2018, Pages 181-192

Case 2

54-year-old woman with a prior history of:

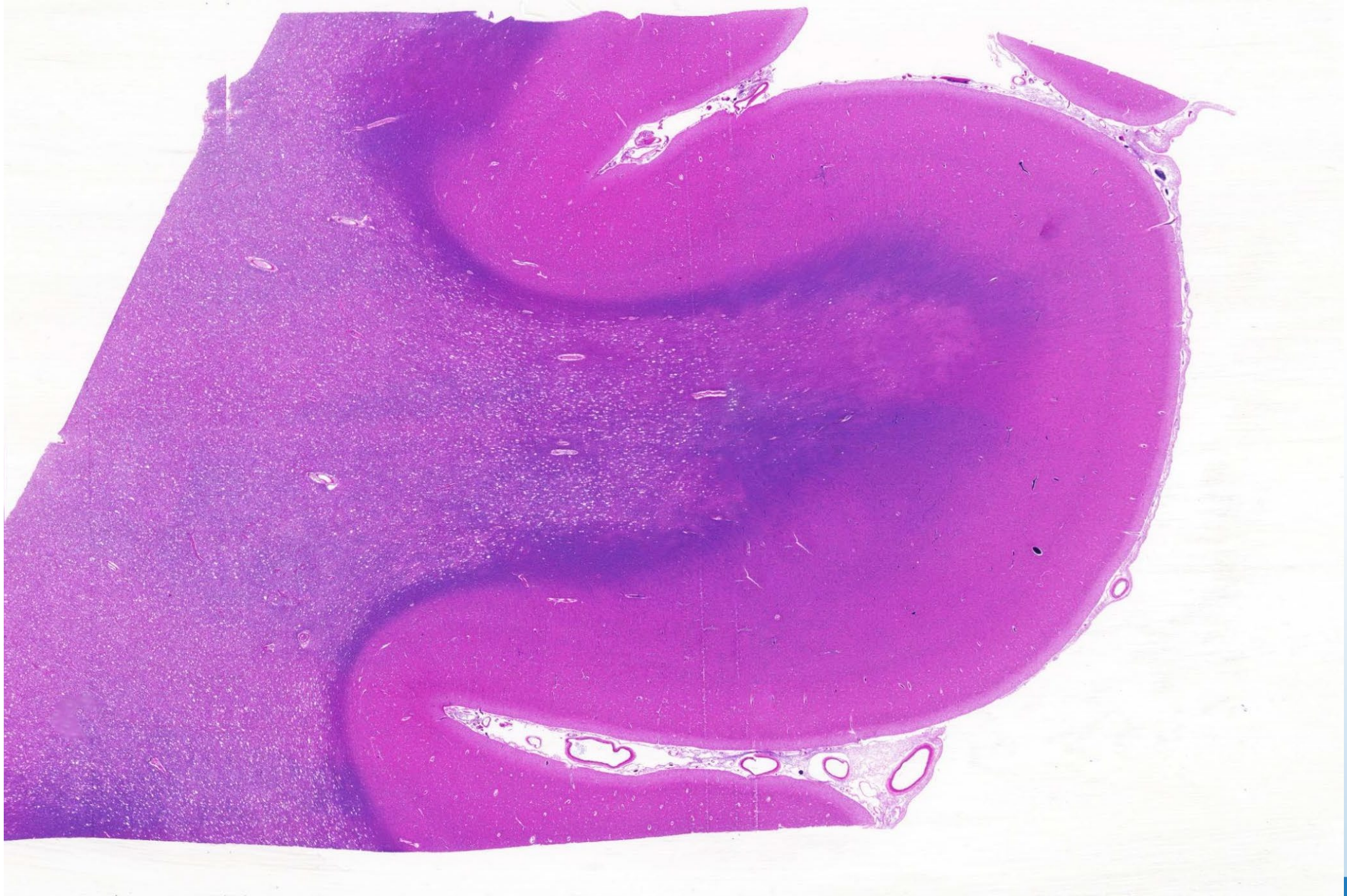
- Polysubstance abuse (ethanol, cocaine, heroin, marijuana)
- 2 pack-per-day smoker
- Post-TBI epilepsy (on levetiracetam and oxcarbazepine)
- Pulmonary embolism (on rivaroxaban)
- Hypertension (on clonidine)
- Back pain (on gabapentin)



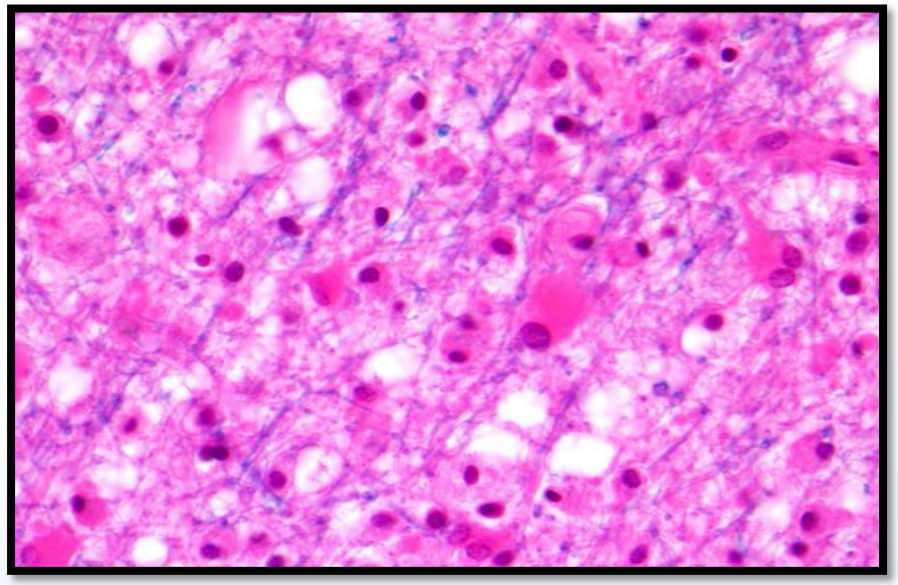
Admitted with vomiting, in the subsequent days developed left hemiparesis, dysarthria and confusion, which led to sedation and intubation.

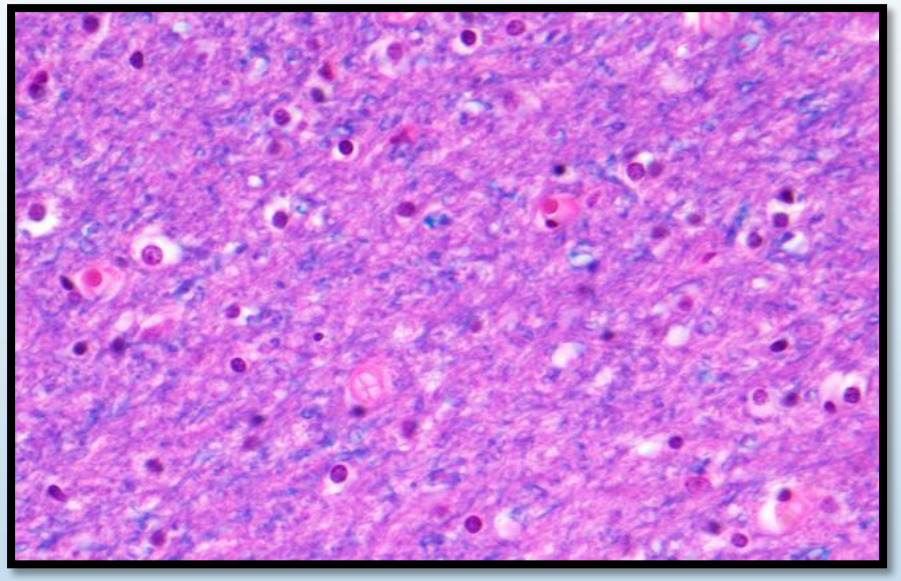
Work up at this time included negative toxicology screen and other negative/normal tests. Per family members, she had been using inhaled heroin in the days prior to symptom onset.

Despite initial improvement, three weeks after presentation she remained nonverbal with somnolence, agitation, and bilateral spasticity.



Heroin inhalation leukoencephalopathy (“Chasing the dragon”)





- Diffuse spongiform and vacuolar white matter change
- Loss of oligodendrocytes, axonal loss, reactive gliosis
- Sparing of U fibers
- Gray matter usually spared

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Cocaine and amphetamines

- Associated with cerebrovascular events in young adults
  - Ischemic infarcts: vasospasm (direct vasoconstriction)
  - Intraparenchymal/subarachnoid hemorrhage: sudden hypertension (50% of cases had underlying lesions)
  - Other potential mechanisms include cardiac arrhythmia and increased platelet aggregation

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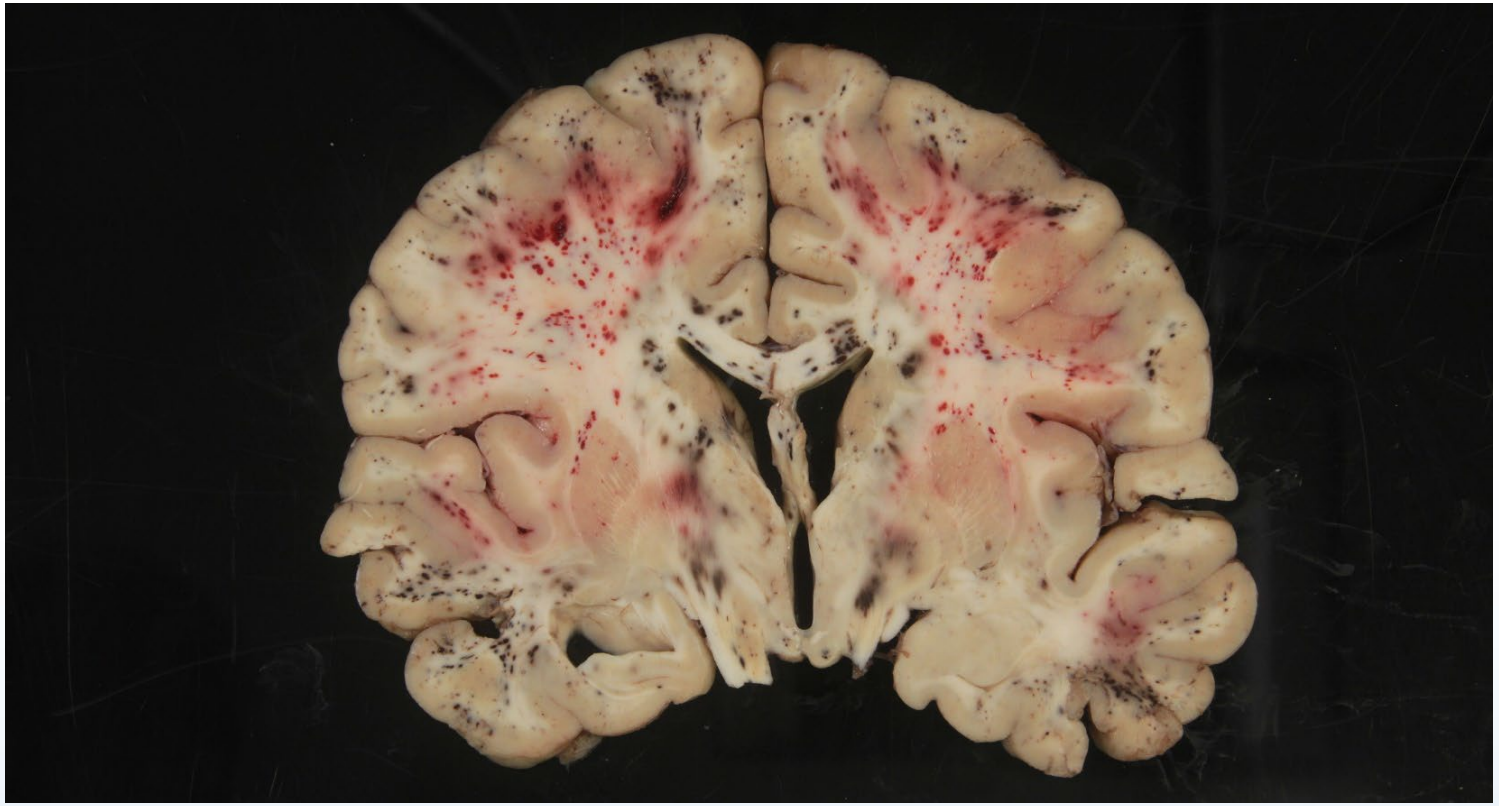


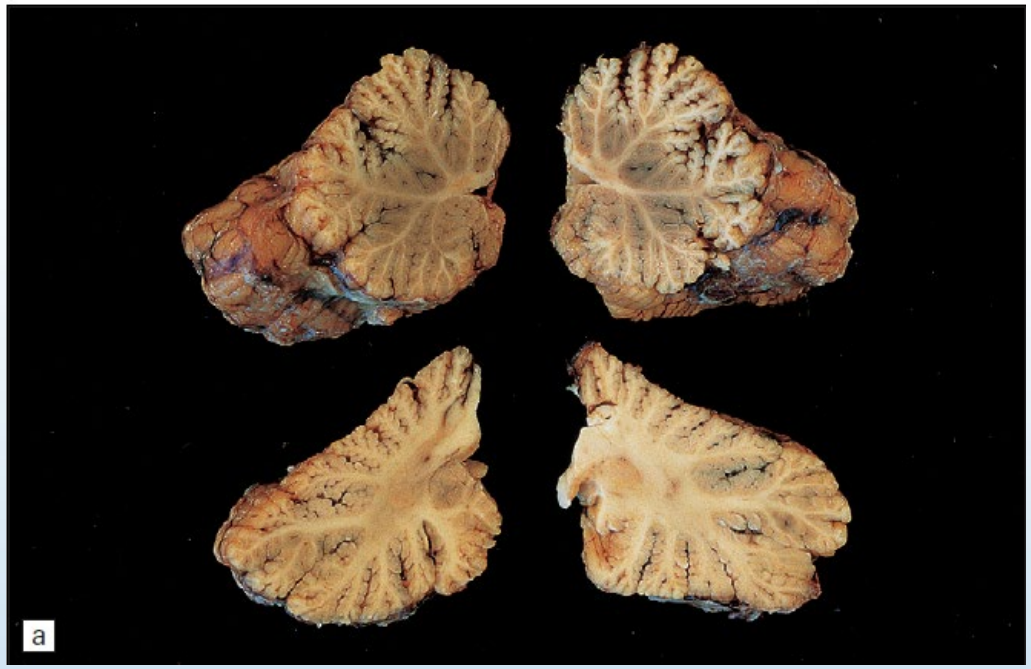
THERAPEUTIC AGENTS

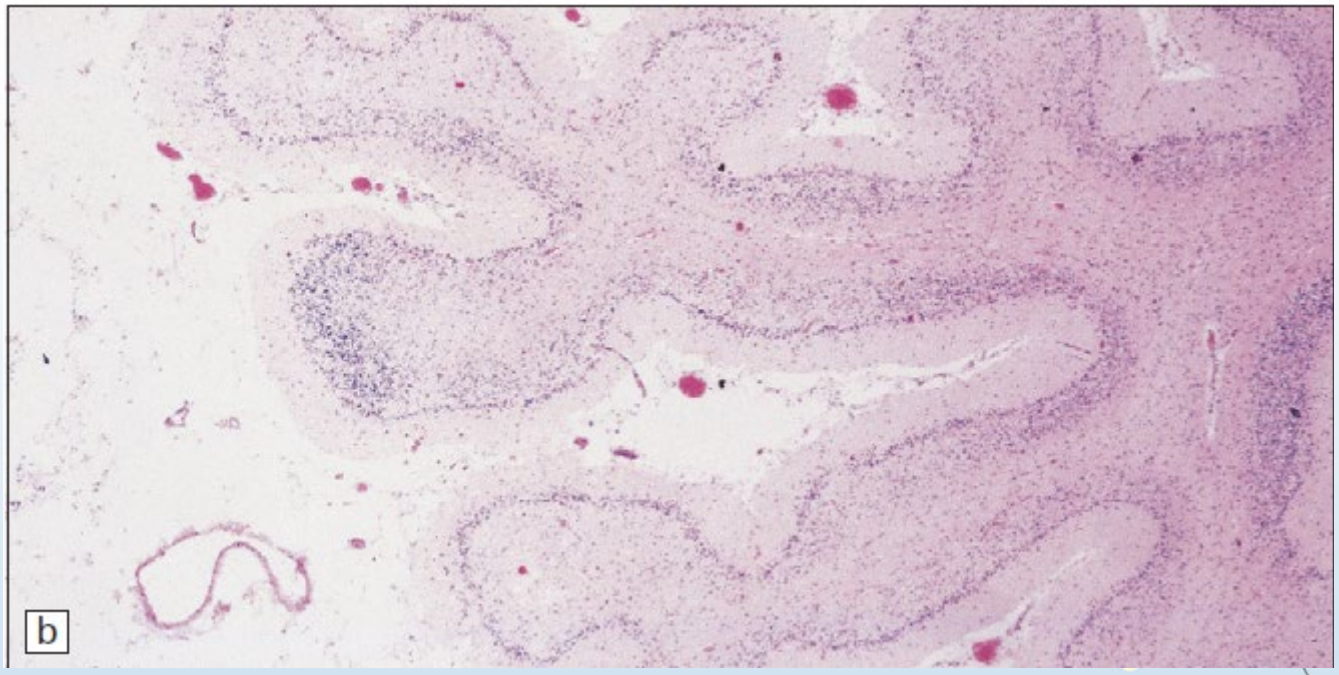
NON-ANTINEOPLASTIC DRUGS

Phenytoin

Dr. Marc del Bigio shared during the live session on 8.27:
The anti-epileptic drug vigabatrin can cause a (probably reversible) vacuolar myelinopathy

- Antiepileptic agent with known cerebellar toxicity
- Loss of Purkinje and granular cells with Bergmann gliosis





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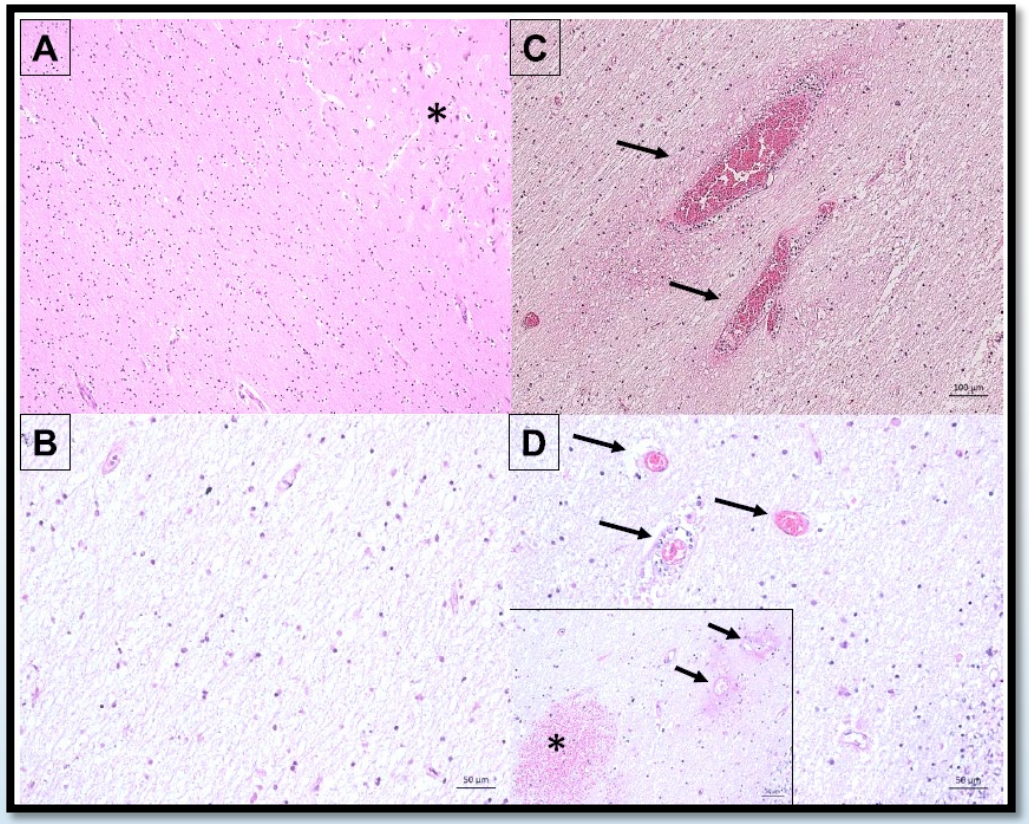
Calcineurin inhibitors (+)

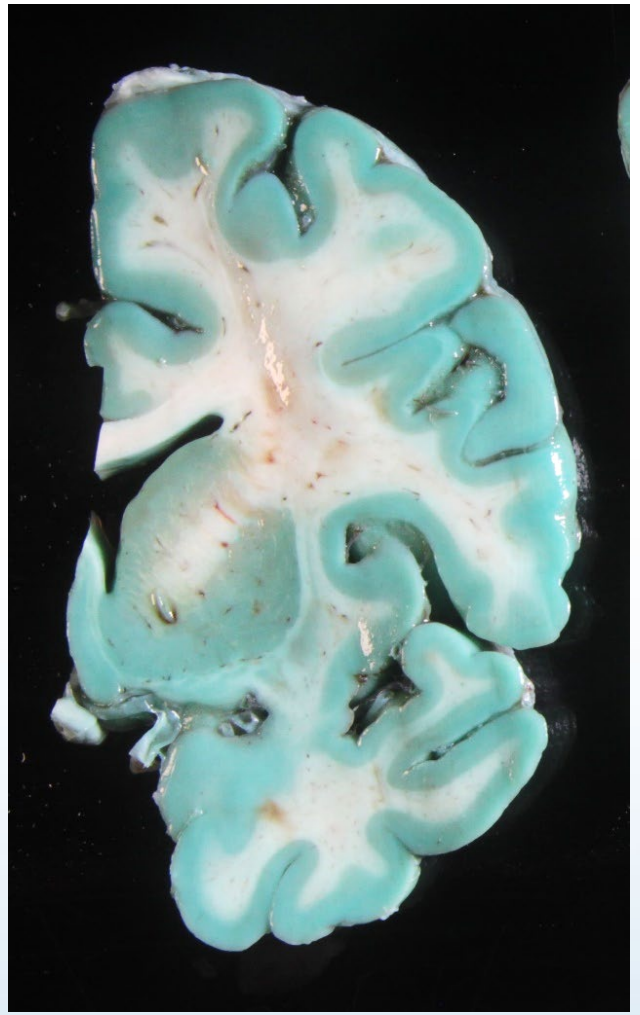


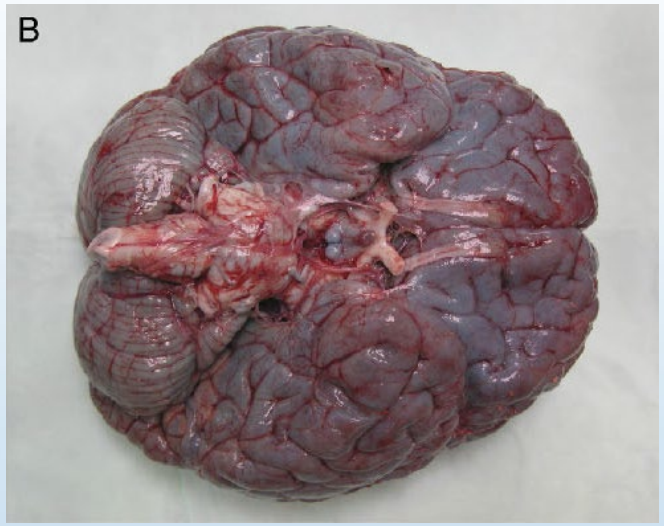
- Immunosuppressants used to prevent transplant rejection and to treat autoimmune and inflammatory disorders
- Examples: cyclosporine, tacrolimus
- Clinical: **posterior "reversible" encephalopathy syndrome (PRES)**
- T2-weighted/FLAIR MRI signal abnormalities in occipital and posterior parietal lobes
- Rare fatal cases: White matter injury with endothelial damage
- (+) Similar findings with malignant hypertension, cisplatin, cytarabine, cyclophosphamide, methotrexate, bevacizumab

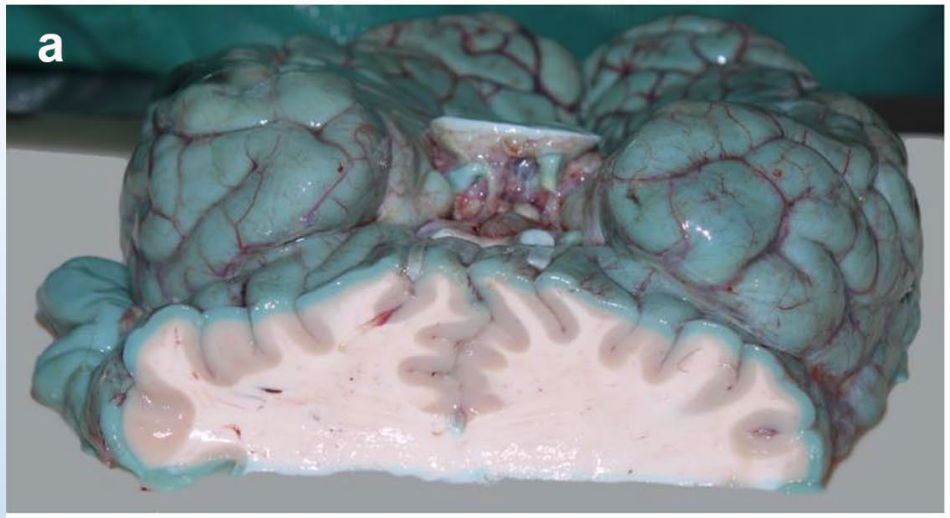
Ismail, F. S., van de Nes, J., & Kleffner, I. (2021). A broad spectrum of posterior reversible encephalopathy syndrome - a case series with clinical and paraclinical characterisation, and histopathological findings. *BMC neurology*, *21*(1), 386.

Methylene blue – “pistachio green”, “avatar” brain

- Often used in therapy-refractory shock
- Effects on the brain clinically innocuous
- Blue coloration darkens with exposure to air (oxidation)
- Detectable as early as 24 hours, persists at least 48 hours after MB administration







Lummus S, Kleinschmidt-DeMasters BK, Methylene Blue “Avatar” Brain, *Journal of Neuropathology & Experimental Neurology*, Volume 72, Issue 3, March 2013, Pages 263–265
Baumgarten J, Greb I, Holz F, Nieß C, Petzel-Witt S, Birngruber CG. Fifty shades of green and blue: autopsy findings after administration of xenobiotics. Forensic Sci Med Pathol. 2024 Oct 30.
Ahrendsen, J. T., & Varma, H. (2021). Green Discoloration of Human Postmortem Brains: Etiologies and Mechanisms of Discoloration. *The American journal of forensic medicine and pathology*, *42*(2), 135–140.

EFFECTS OF RADIATION IN THE CNS

Radiation injury

- Up to 24% incidence with conventional doses
- Rare if cumulative <50-60 Gy (brain) or 45 Gy (spinal cord)
- Acute and early delayed toxicity
  - BBB dysfunction --- cerebral edema
  - Mostly transient and reversible
- Late delayed toxicity (radiation necrosis)
  - Direct injury to glia, neurons, and endothelium
  - Often irreversible
- Pseudoprogression: contrast enhancing lesions appearing 2-6 months after chemoradiation in patients with high-grade gliomas, which improve or stabilize over time

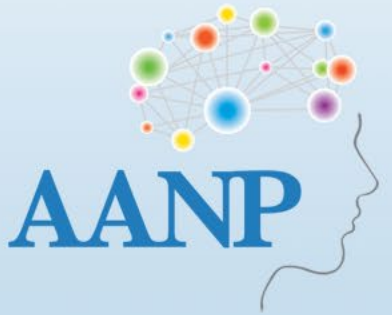


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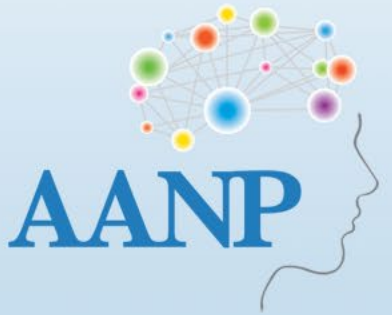
TABLE 59.1 Changes favouring treatment-induced necrosis/pseudoprogression* vs recurrent/progressive tumour

Clinical feature	Treatment-induced necrosis/ pseudoprogression	Tumour recurrence/progression
Patient symptoms	No new symptoms	Worsening neurological status
Imaging feature		
Standard MRI	Rim-enhancing 'Swiss cheese' or 'soap bubble' patterns, limited mass effect	Rim-enhancing; homogeneous hypointense centre
DWI/ADC/DTI	Heterogeneous, hypointense	Hyperintense (especially at margins)
Perfusion MRI	Decreased rCBV	Increased rCBV
H-MRS	All peaks decreased, except for lactate and/or lipid (necrosis)	Increased choline in regions of cellular tumour (Cho/Cr and NAA/Cr ratios >1.8)
PET	Decreased metabolism	Increased metabolism
Histological feature		
Necrosis	Large infarct-like zones with hypocellular edges and dystrophic calcifications	Large or microscopic foci with hypercellular or palisading edges
Blood vessels	Telangiectatic Hyalinised Angionecrotic	Microvascular proliferation with enlarged and multilayered endothelial lining
Adjacent brain parenchyma	Rarefied or vacuolated, pale, and gliotic with vascular changes listed earlier	Nearly normal or infiltrated by individual tumour cells
Cytological atypia	Bizarre bubbly nuclei and abundant cytoplasm	High N : C ratio
Mitotic figures and proliferation rate	Rare mitoses, low proliferation rate	Frequent mitoses (if tumour is high-grade), moderate to high proliferation rate



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Radiation injury – long-term sequelae

- Vascular malformation-like lesions
- Stroke-like migraine attacks after radiation therapy (SMART syndrome)

- Radiation-induced leukoencephalopathy
  - Disseminated
  - Secondary to whole brain irradiation (currently rare)

- Radiation-induced neoplasms

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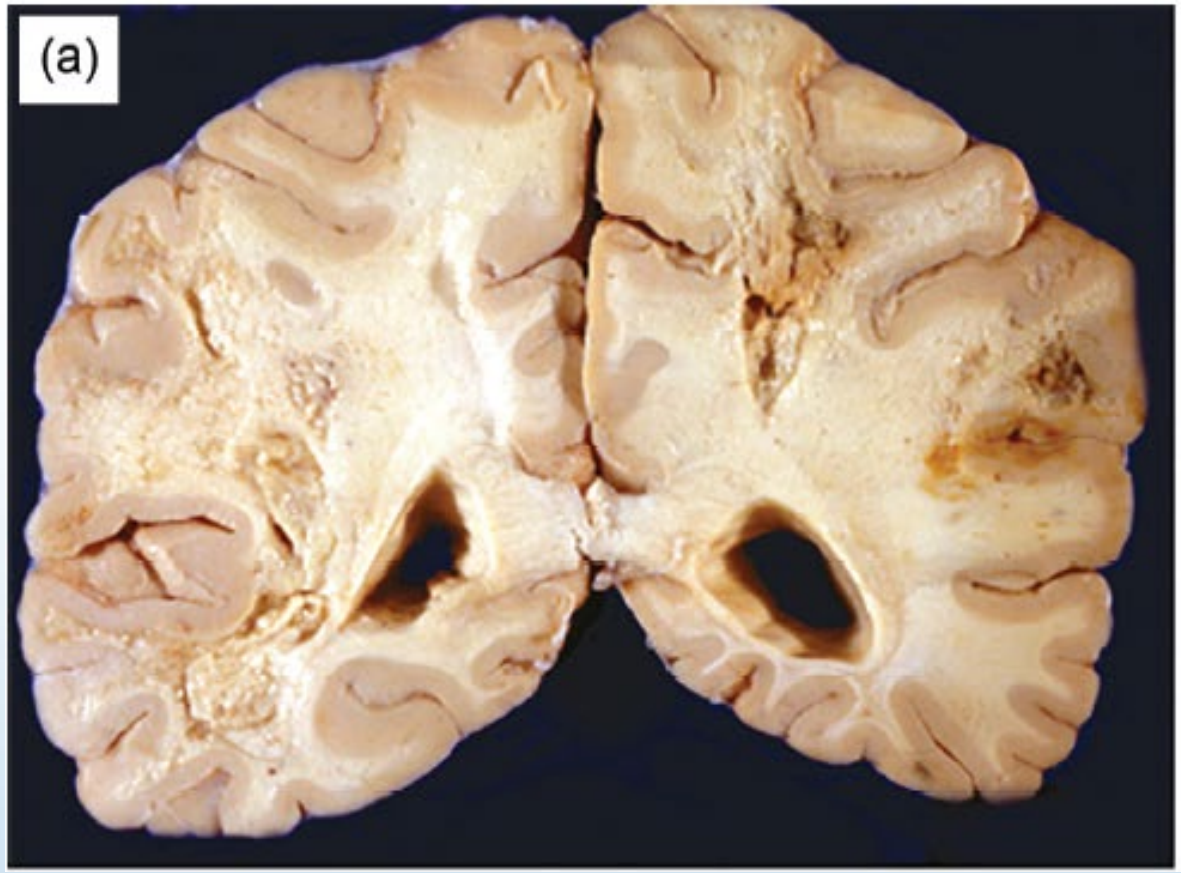
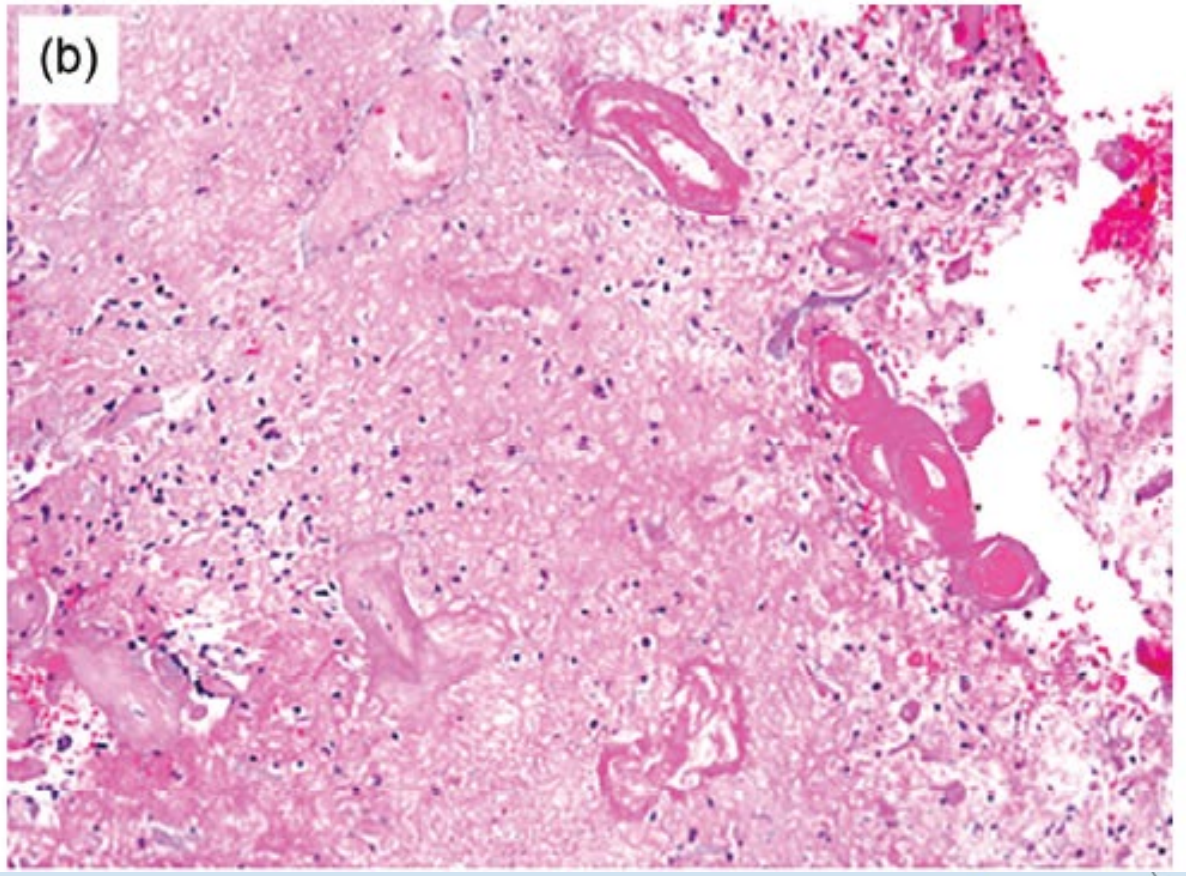
Radiation-induced leukoencephalopathy





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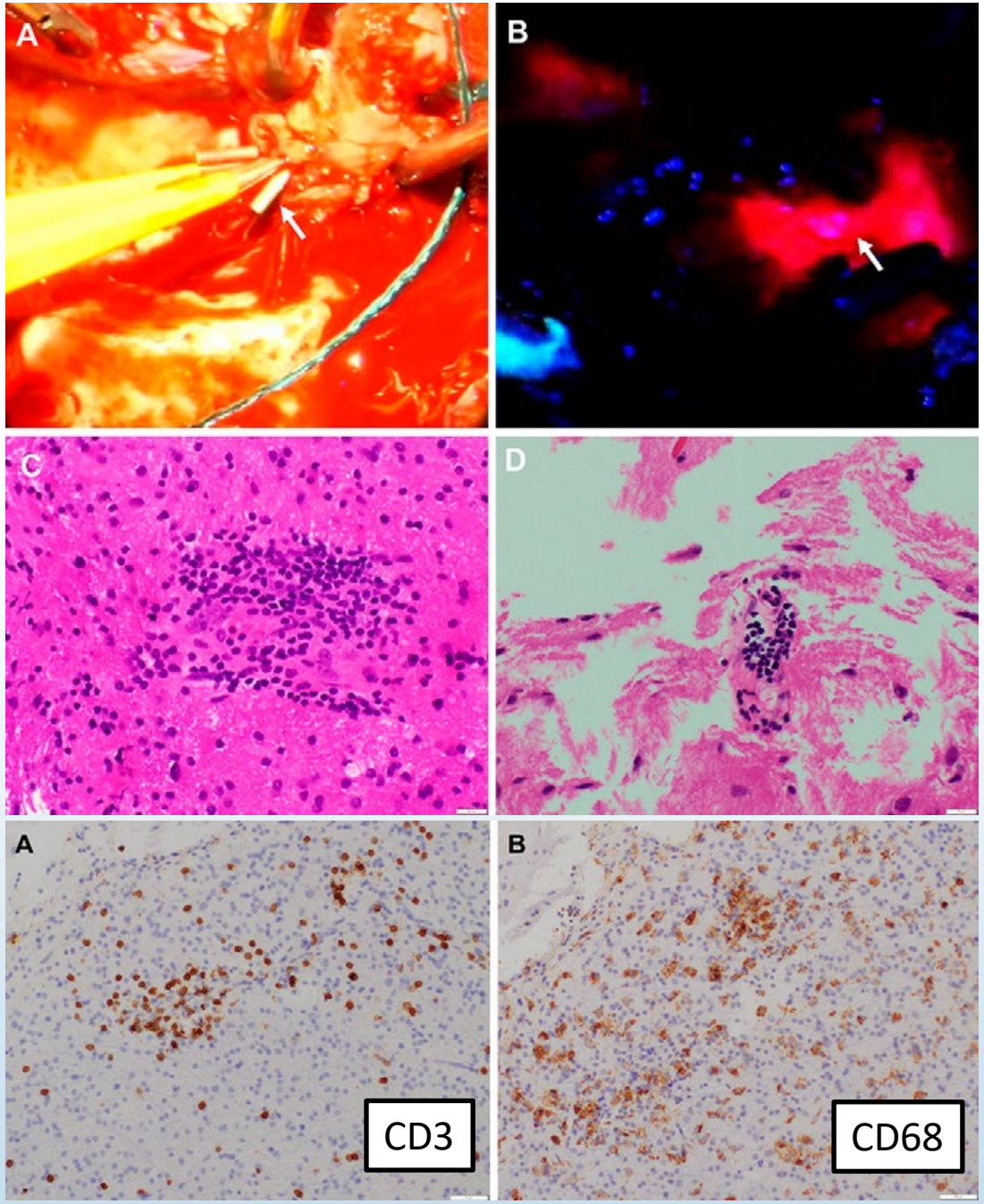
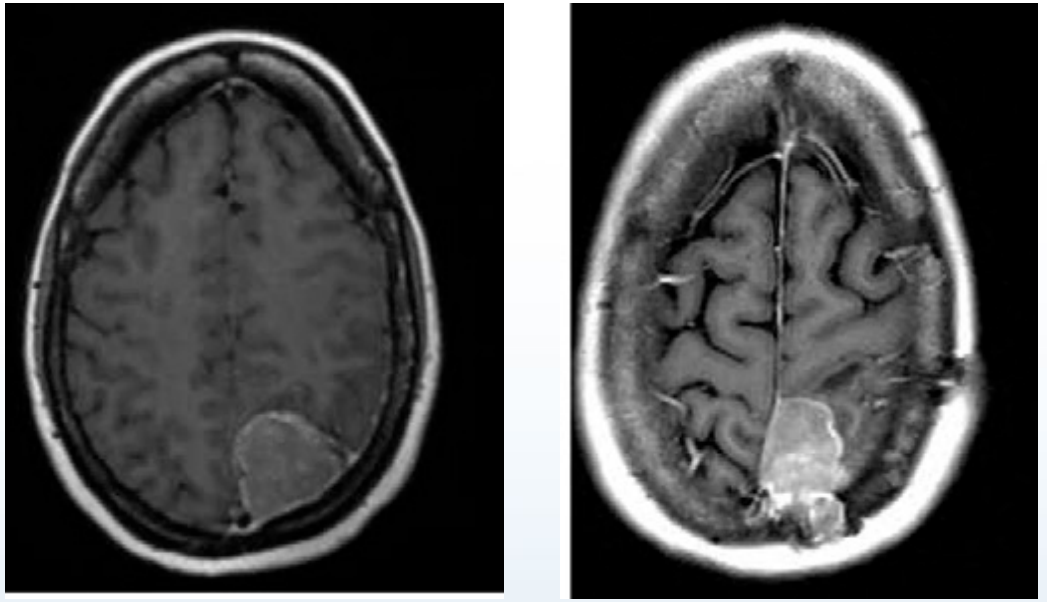


Fluorescence and immune-cell infiltration of nonneoplastic, postbrachytherapy brain tissue in 5-ALA–guided resection of recurrent anaplastic meningioma: illustrative case



Ramapriyan R, Clark VE, Martinez-Lage M, et al. J Neurosurg Case Lessons. 2024 Feb 26;7(9):CASE23550.

CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agents

- Direct effect on the CNS / indirect effect from systemic therapy
- Developing and aging nervous system more vulnerable
- Methotrexate and others cause white matter toxicity
- Synergistic effect with combinations
- “Chemo brain” – chemotherapy-induced cognitive dysfunction, usually mild and reversible
- Disruption of neurogenesis, gliogenesis, myelin integrity

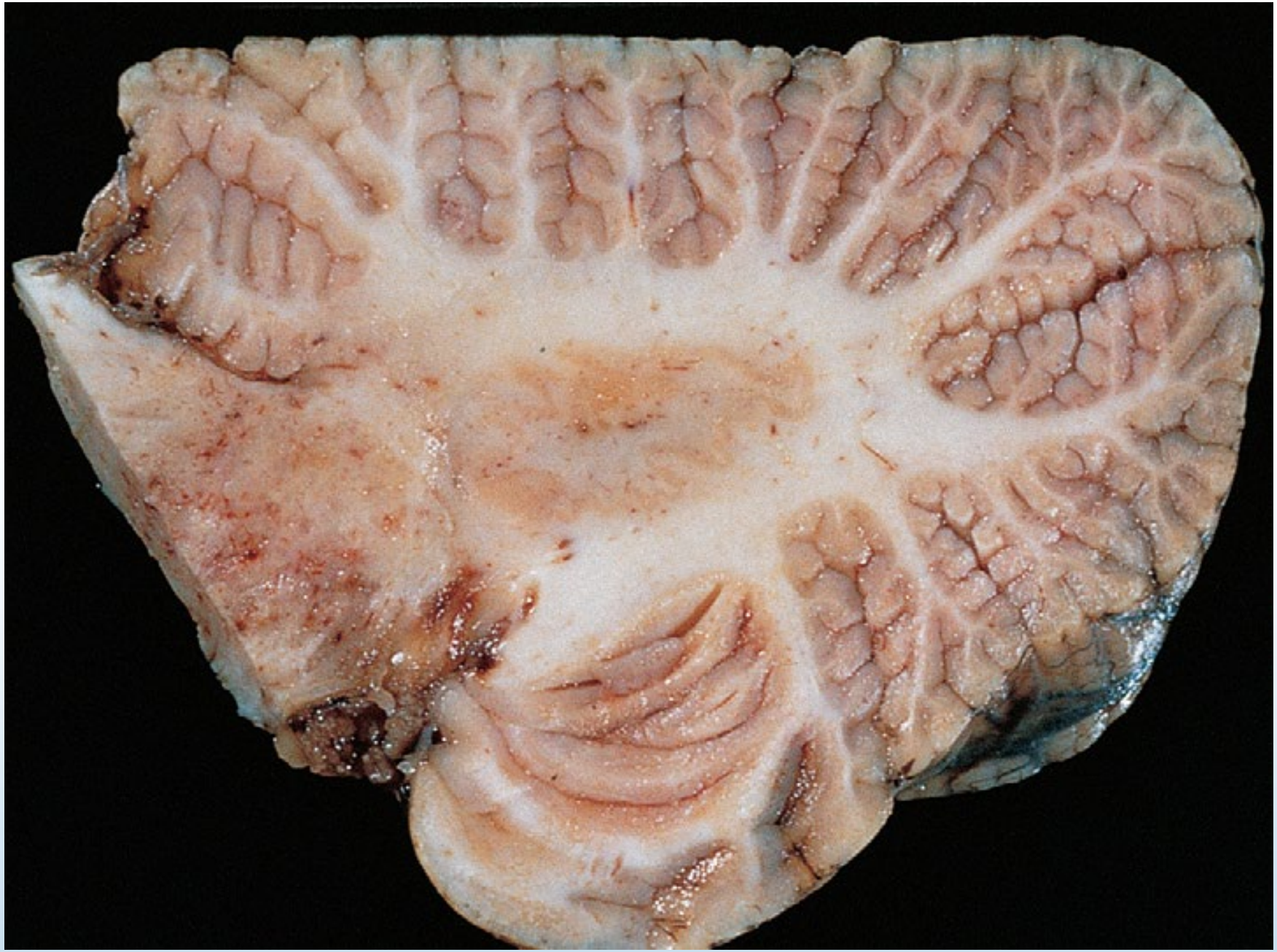
Case 3

A 5-month-old infant with acute lymphoblastic leukemia was treated with combination chemotherapy including methotrexate.

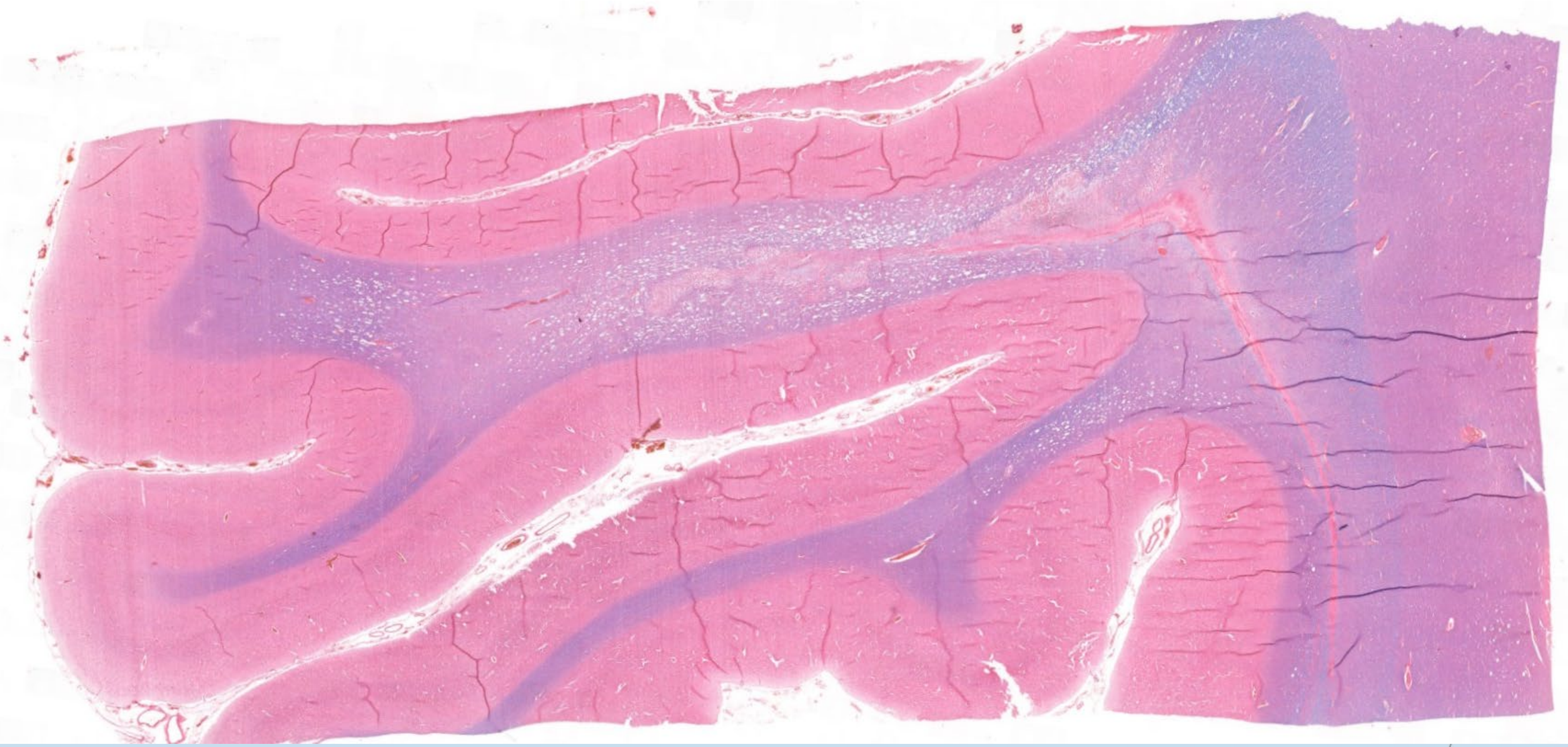
After initial remission, at 22 months she developed leptomeningeal involvement and was treated with intrathecal methotrexate with improvement.

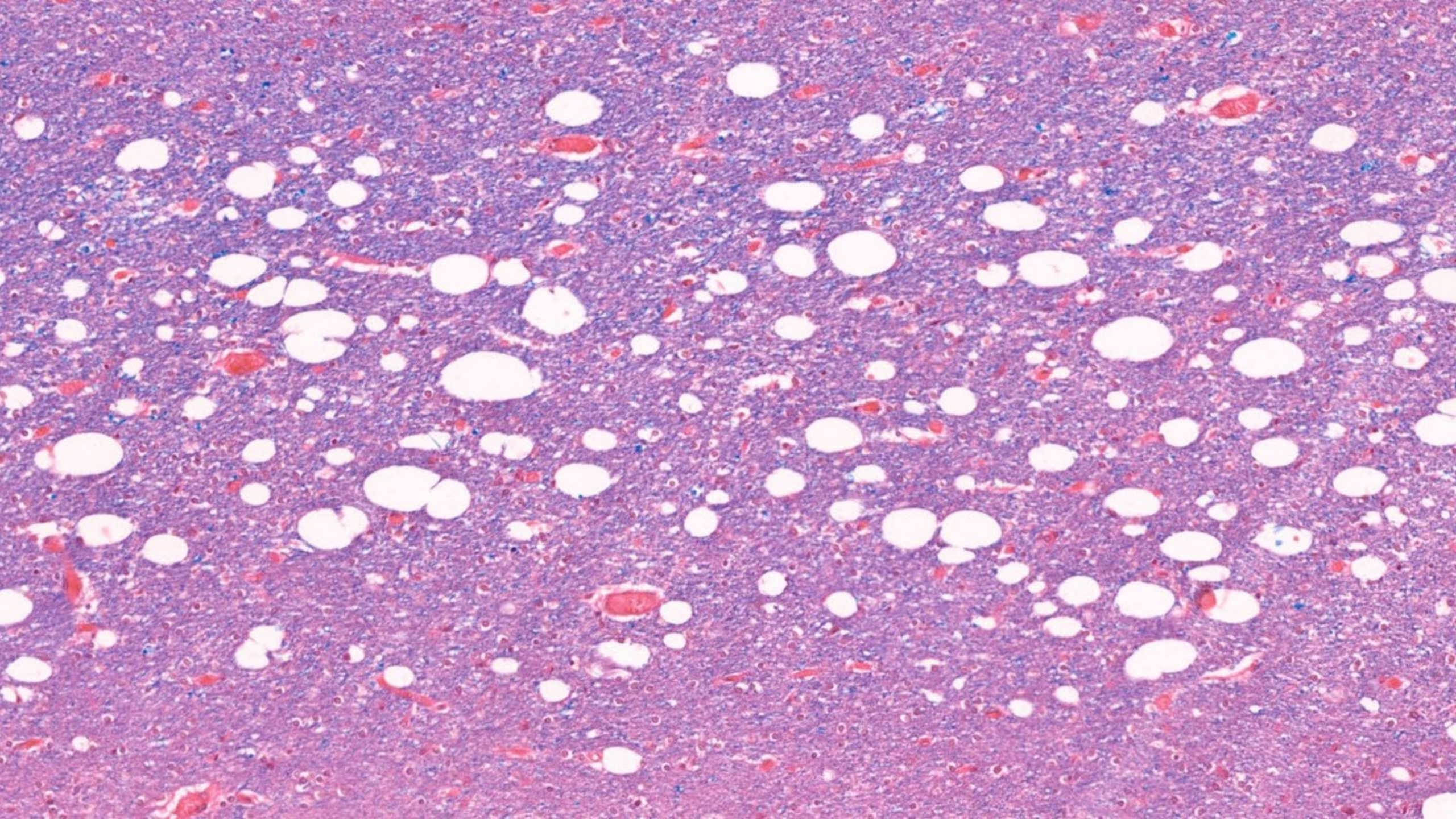
She developed subsequent CNS relapse three times, also treated with increasing doses of intrathecal methotrexate in combination with other agents. At this time there was CT evidence of “generalized decreased density of the white matter” and “small foci of enhancement”. Whole brain irradiation was administered.

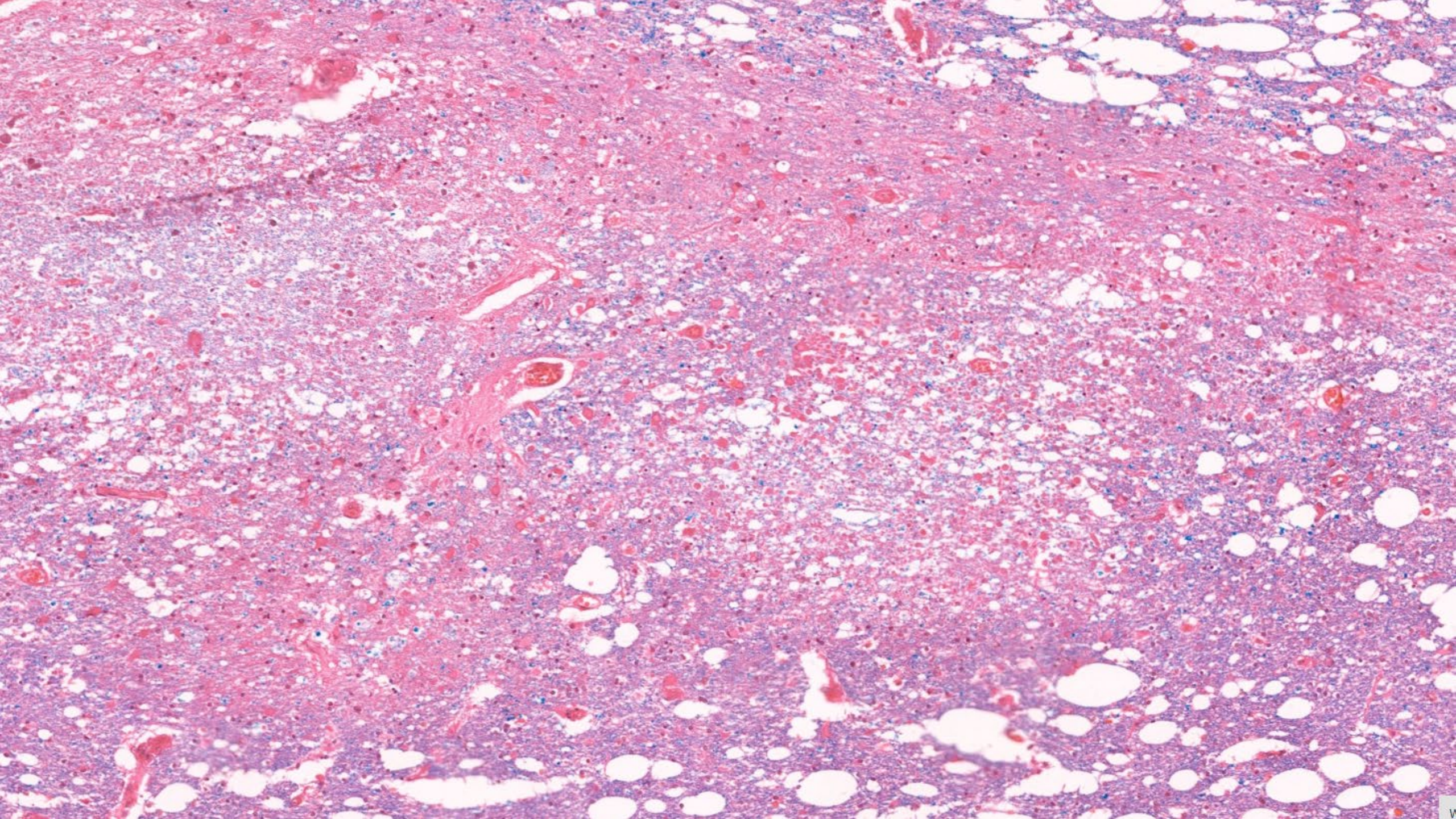
Over several months her neurological clinical symptoms progressed, with gait ataxia, mutism, nystagmus, and severe dysphagia. She died at age 6 and an autopsy was performed.

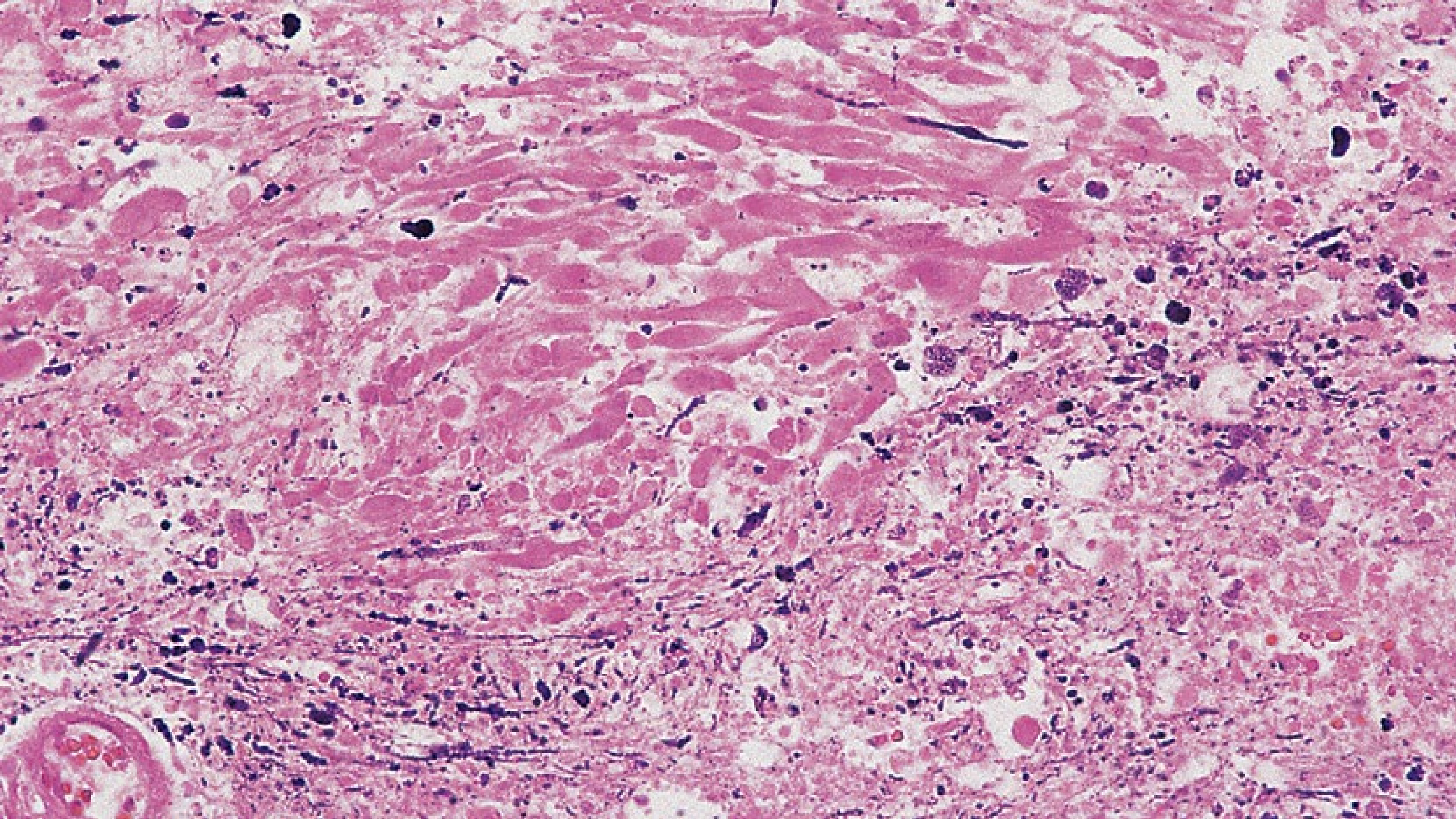


Chapter 25 in: Love,, David Ellison, Brian Harding, James Lowe, Harry V. Vinters, Leila Maria Cardao Chimelli, S. Neuropathology. Available from: Elsevier eBooks+, (3rd Edition). Elsevier - OHCE, 2014.

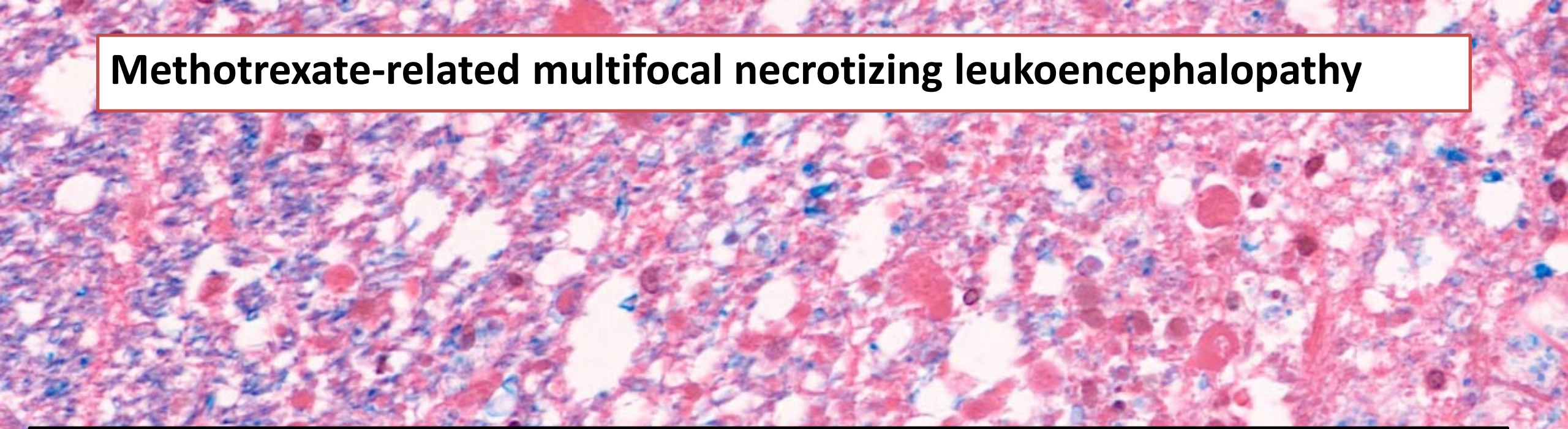




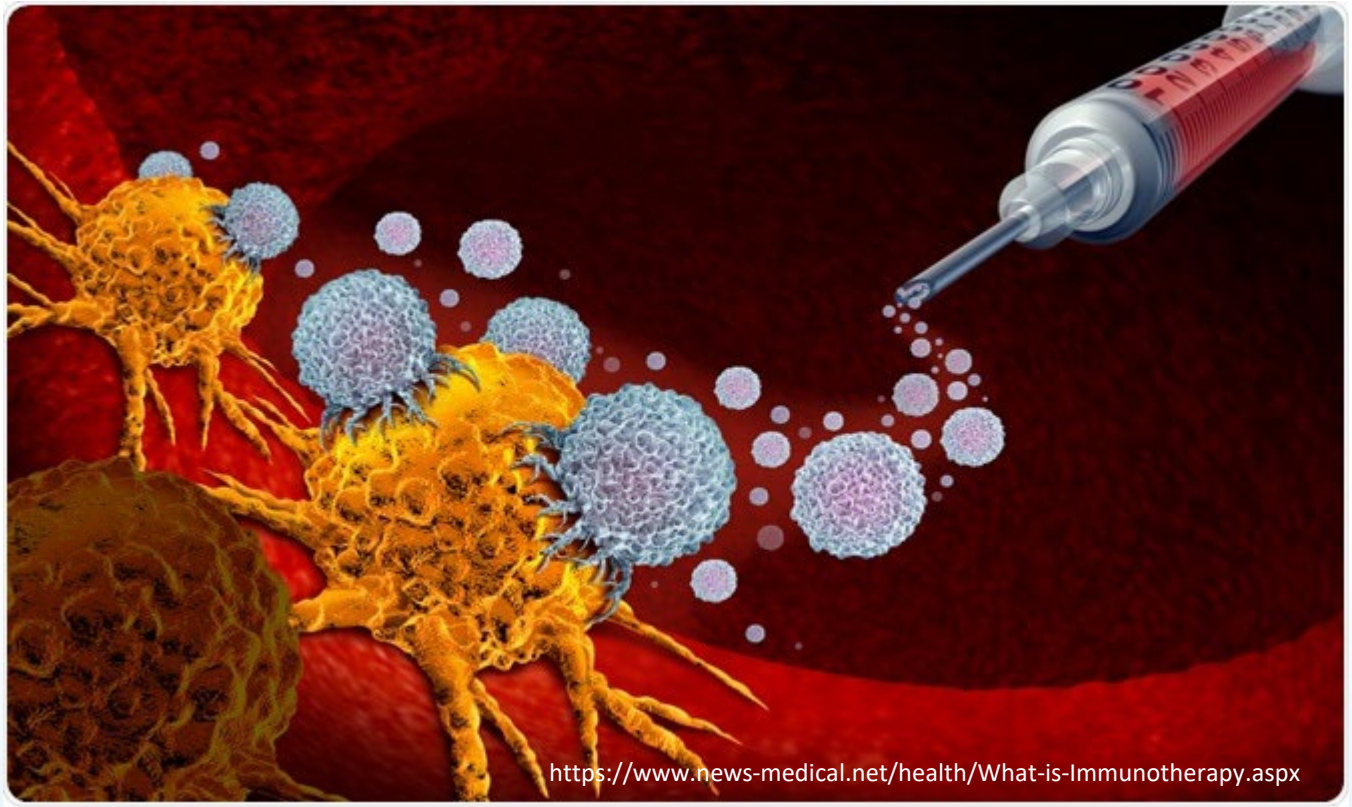




Methotrexate-related multifocal necrotizing leukoencephalopathy



- Miliary rounded to confluent foci of white matter injury
- Mostly cerebral white matter, can affect posterior fossa
- Prominent spongiosis, oligodendrocyte loss, necrosis
- Markedly swollen axons - prominent axonopathy (differentiates from radiation leukoencephalopathy)
- Microcalcifications



IMMUNOTHERAPIES

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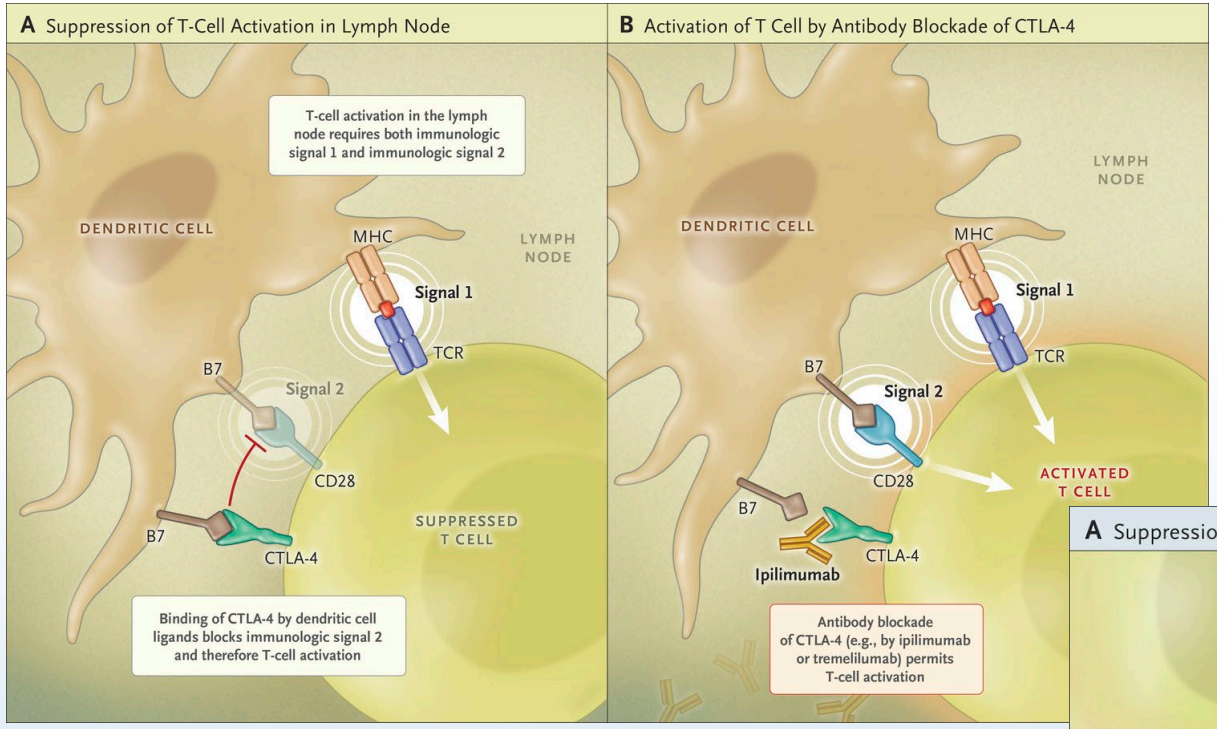
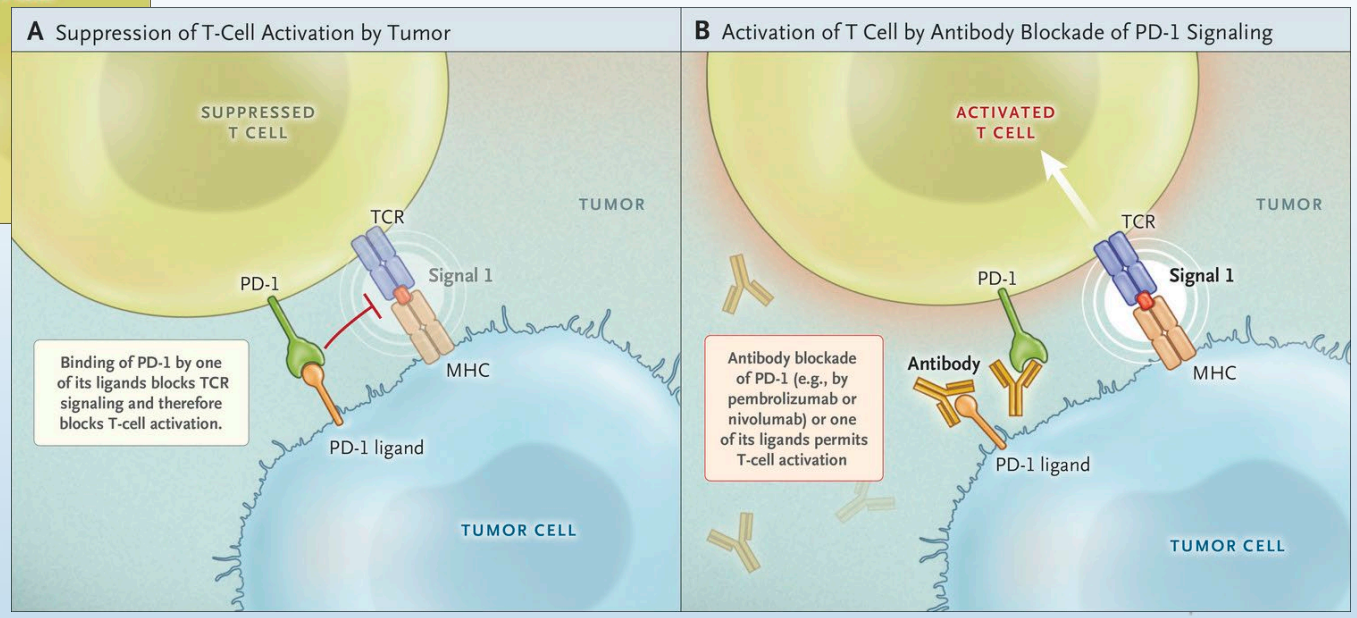
Immunotherapy – Immune checkpoint inhibitors

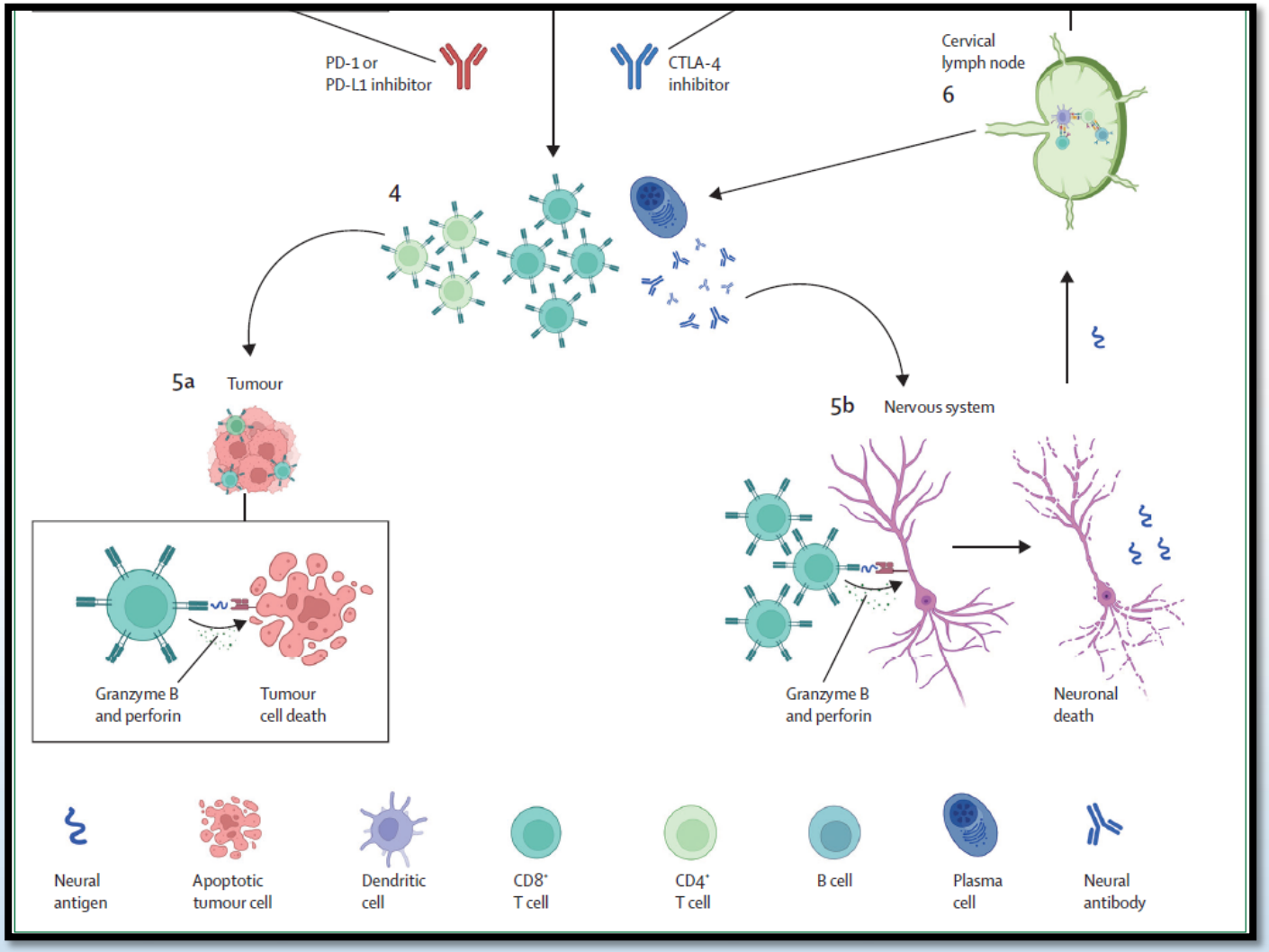


- T-cell activation in the lymph node (“early”) regulated by **CTLA-4**
- T-cell activation in peripheral tissues (“late”) mediated by **PD-1** signaling.



Ribas A. N Engl J Med 2015;373:1490-1492.

Immunotherapy – Immune checkpoint inhibitors



Immune-related adverse events (irAE)

- Off-target toxicity (on-target, off-tumor)
- May affect any organ system

- T-reg cell disfunction
- Enhanced natural killer cell activity
- Indirect promotion of antibody production by B-cells
- Exacerbation of a prior autoimmune condition/Development of a novel autoimmune response
- Cross reactivity with autoantigens (molecular mimicry)

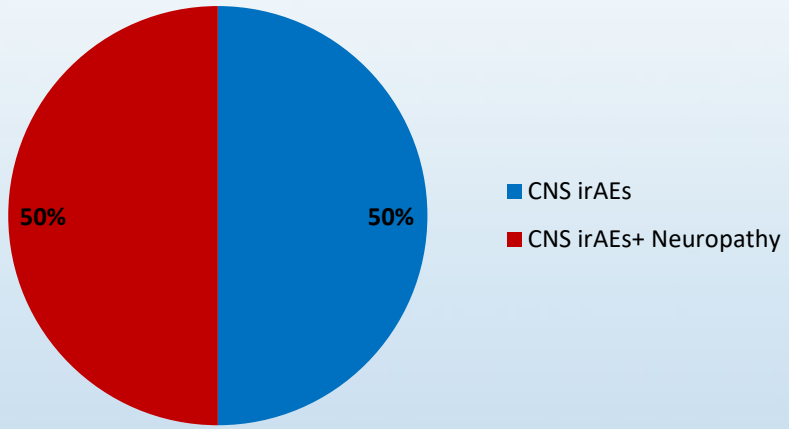
AANP

Farina, A., Villagrán-García, M., Vogrig, et al. (2024). Neurological adverse events of immune checkpoint inhibitors and the development of paraneoplastic neurological syndromes. *The Lancet. Neurology*, *23*(1), 81–94.

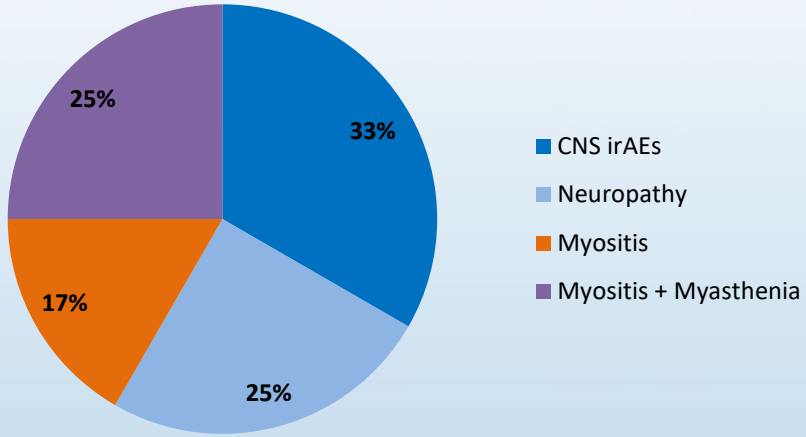
Severe Neurological Toxicity of Immune Checkpoint Inhibitors: Growing Spectrum

- 1851 patients received ICIs between 2011 and 2017
- 28 patients (**1.5%**) developed moderate to severe neuro irAE (grades 3-4)
- Combination therapy > anti-CTLA4 > anti-PD1/PDL1 monotherapy
- 70% within cycles 1-4
- Peripheral nerve involvement most common

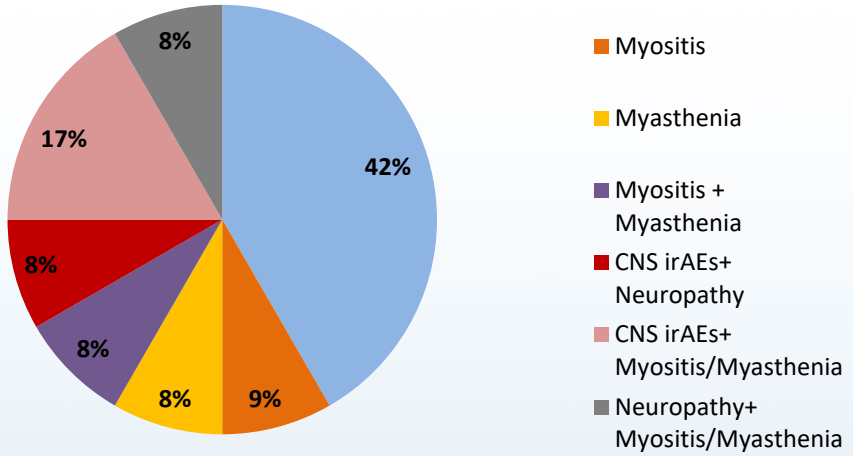
CTLA4 (n=4)



PD1/PDL1 (n=12)



PD1 and CTLA4 combination (n=12)



Dubey, D., David, W. S., Reynolds, K. L., et al. (2020). *Annals of neurology*, *87*(5), 659–669.

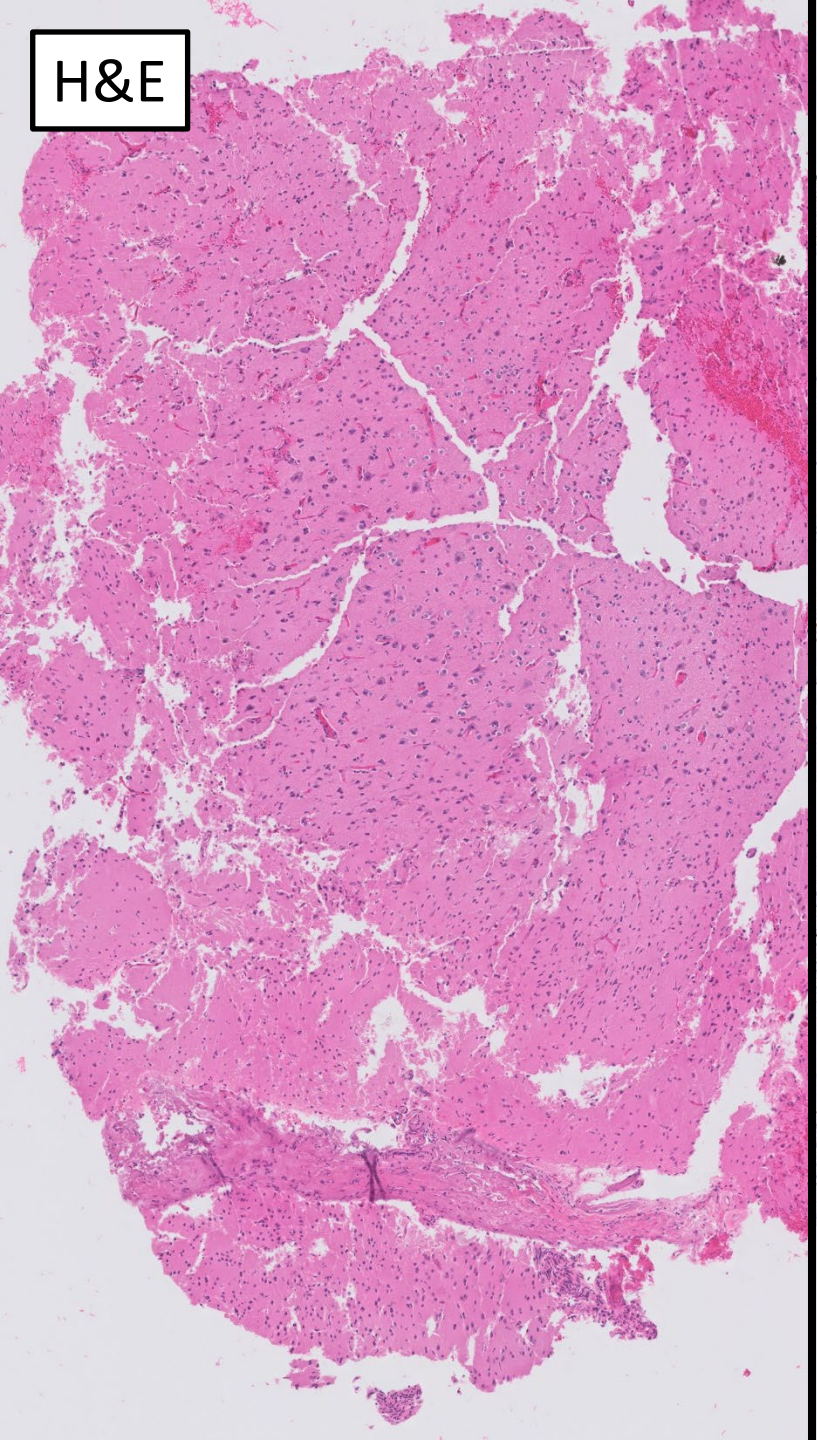
Case 4

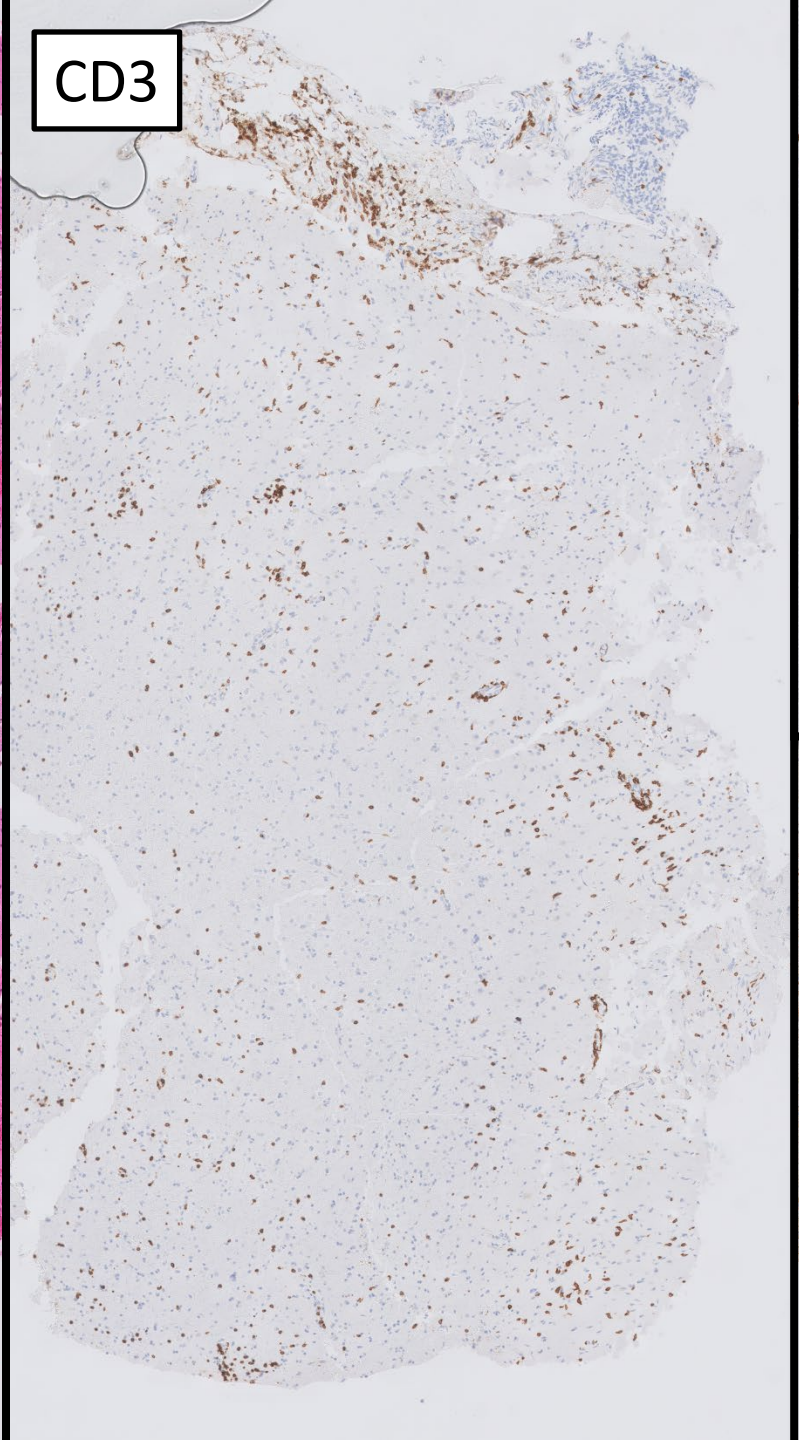
A 71-year-old man was diagnosed with melanoma and three years later developed metastatic disease. He received treatment with pembrolizumab.

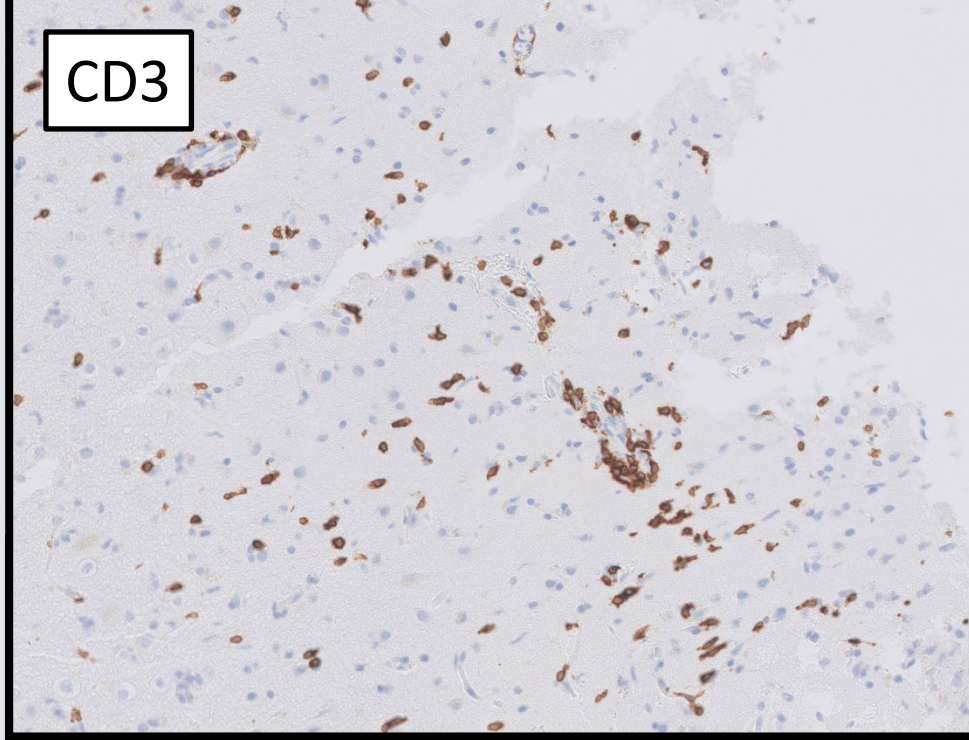
After three cycles, he developed a subacute progressive encephalopathy resulting in akinetic mutism, with concomitant symptoms of peripheral neuropathy.

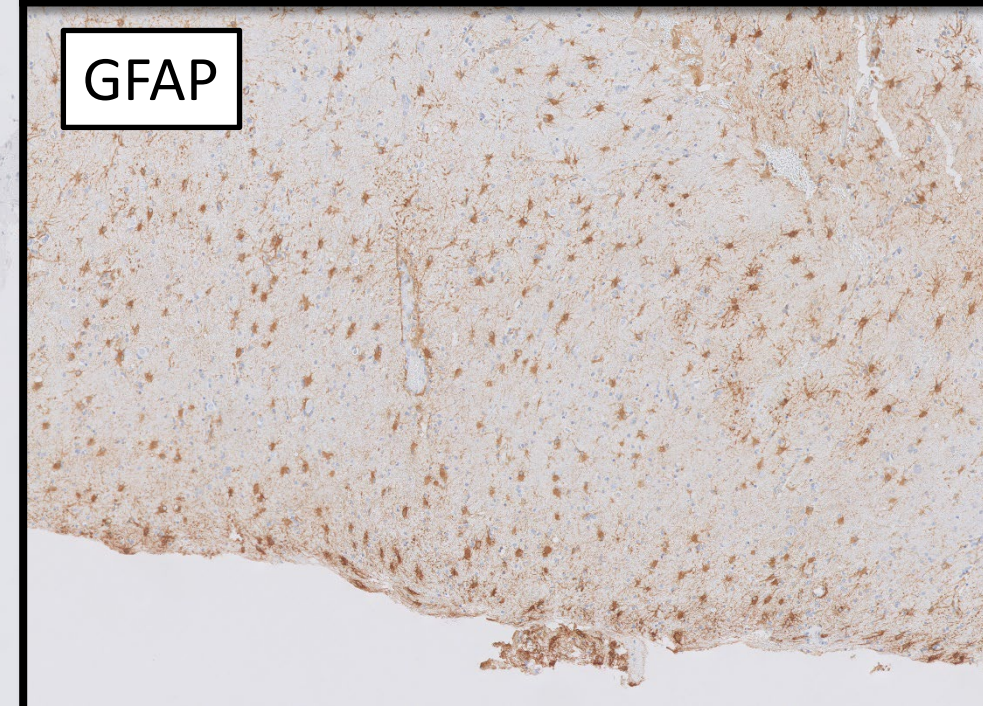
Stopping ICI, empiric treatment with steroids and IVIG lead to stabilization but no definitive improvement.

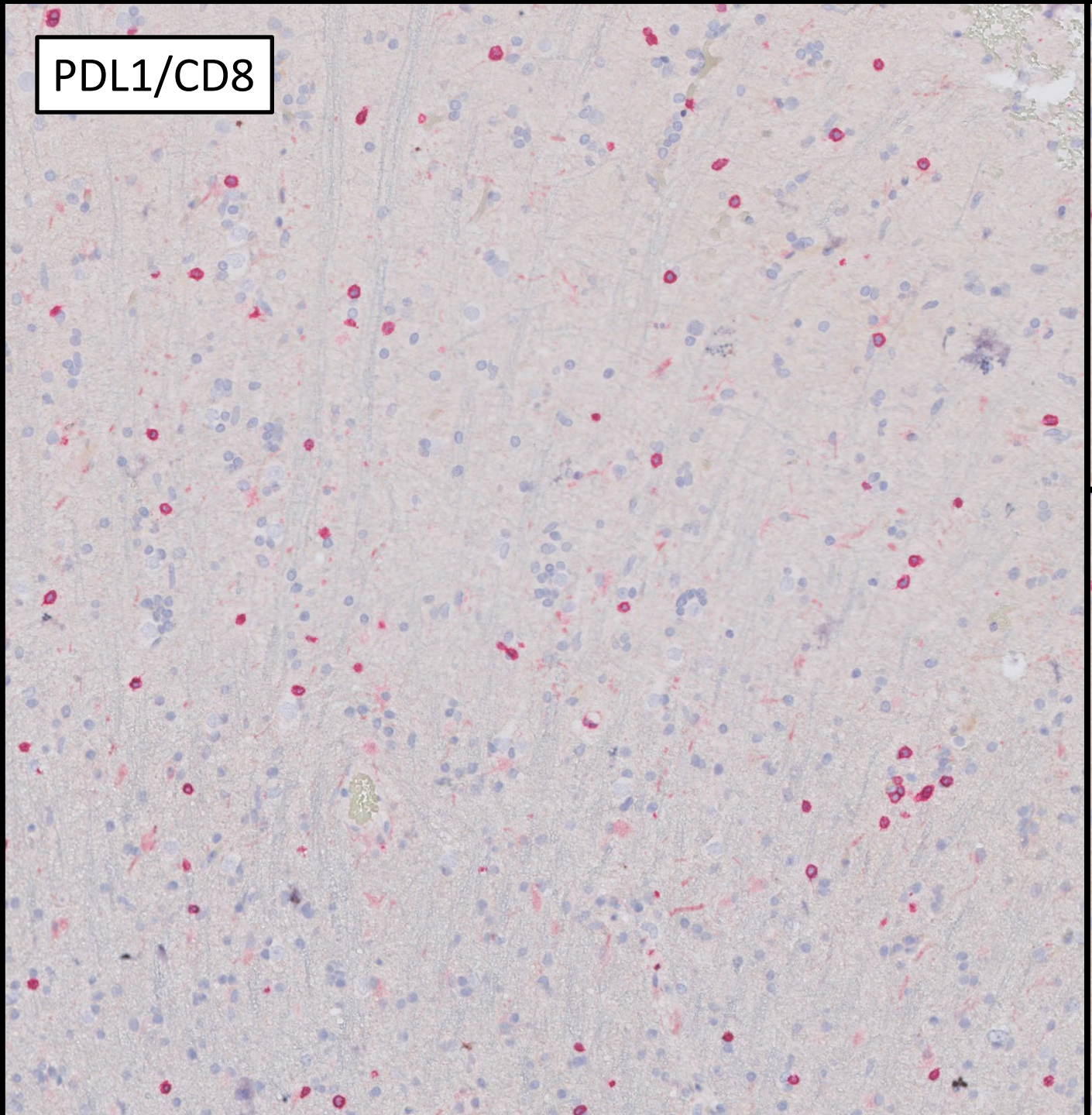
A brain biopsy was obtained.

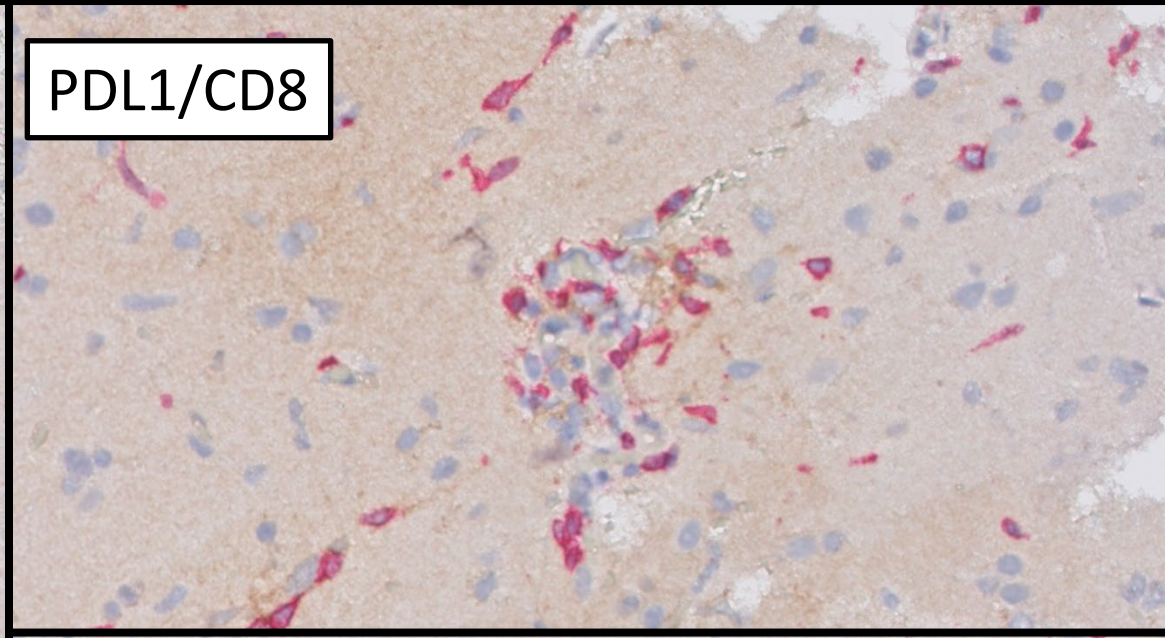

H&E

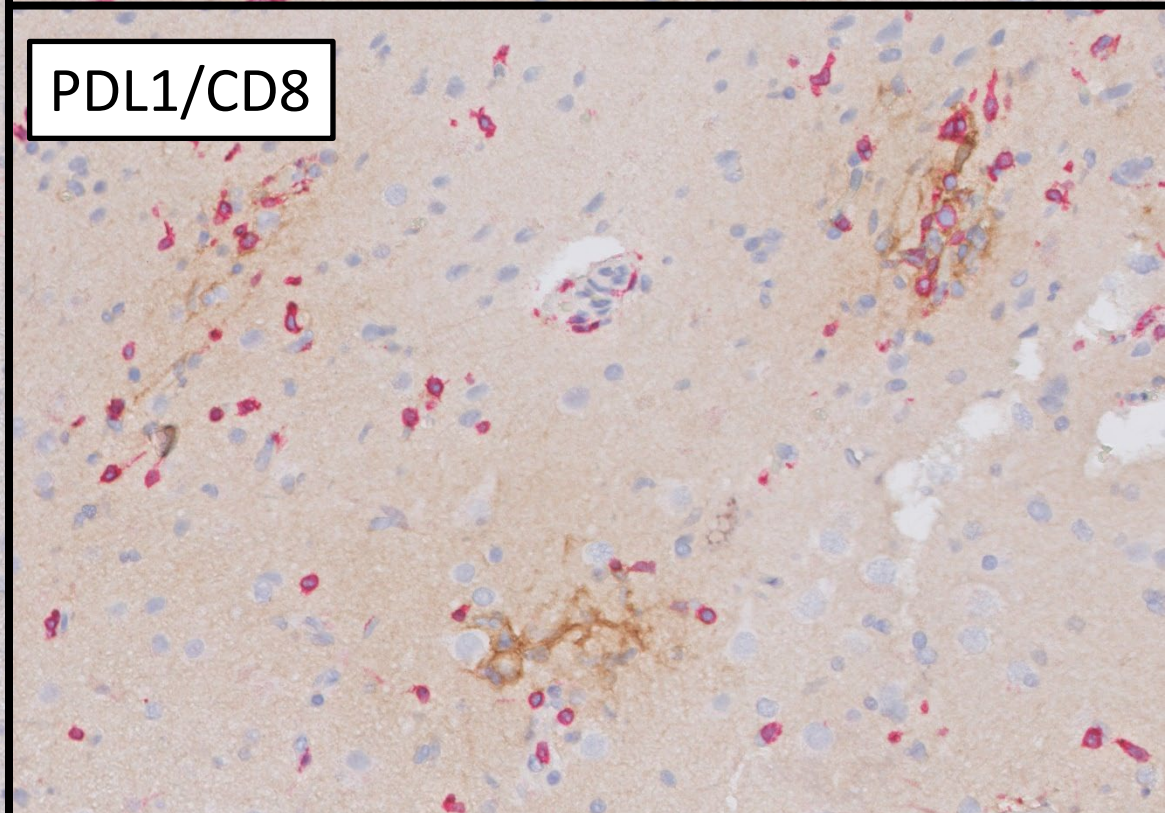

CD3


CD3

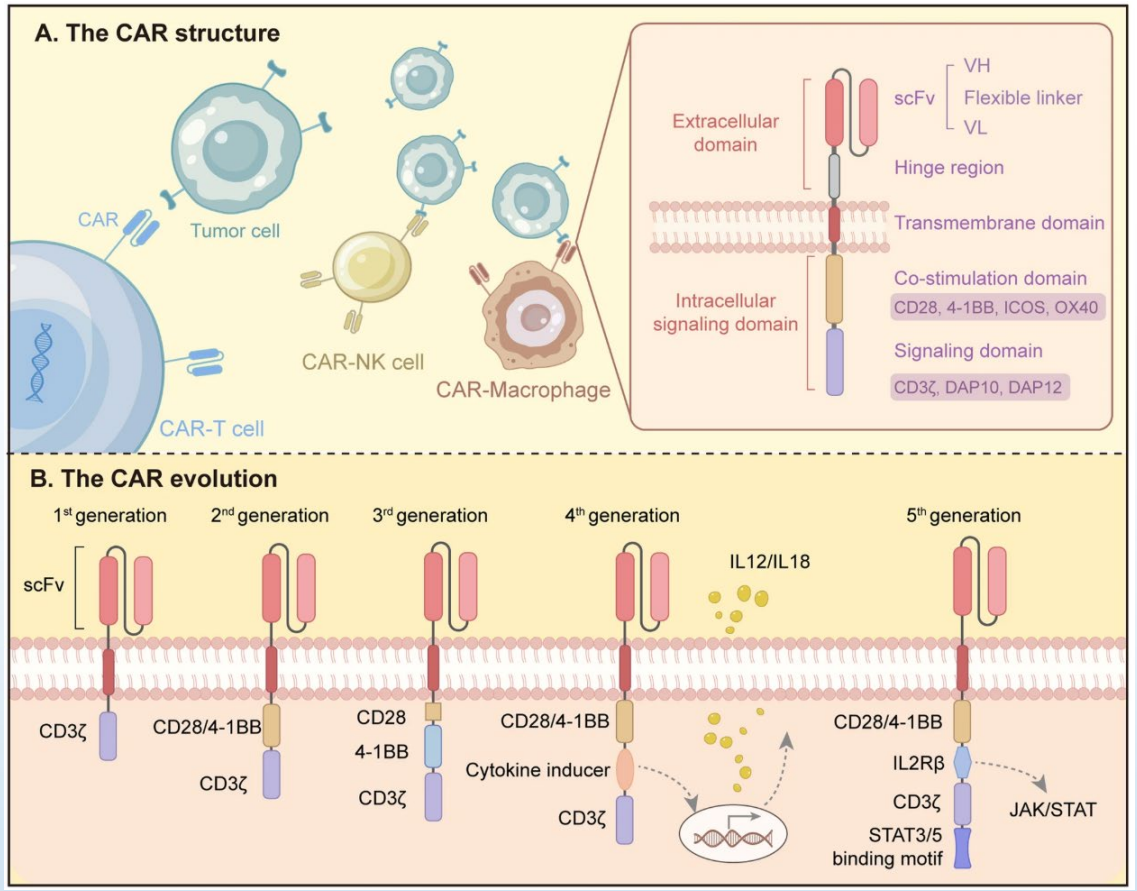

GFAP


PDL1/CD8


PDL1/CD8


PDL1/CD8

Immunotherapy – adoptive cell therapies



- Chimeric Antigen Receptor (CAR) T Cell Therapy

- Tumor-Infiltrating Lymphocyte (TIL) Therapy
- Engineered T Cell Receptor (TCR) Therapy
- Natural Killer (NK) Cell Therapy

Qin, H., Zhou, Z., Shi, R. *et al.* Insights into next-generation immunotherapy designs and tools: molecular mechanisms and therapeutic prospects. *J Hematol Oncol* **18**, 62 (2025).

Immunotherapy - Chimeric Antigen Receptor (CAR) T Cell Therapy

- Target antigens
  - CD19 (B-cell lymphomas, B-ALL)
  - CD22 (pre-B-ALL)
  - BCMA (multiple myeloma)

- Targets in CNS tumors
  - CD19 (PCNSL/SCNSL)
  - EGFRvIII
  - GD2
  - IL-13Rα2
  - HER-2
  - B7-H3
  - EphA2

- Overall toxicity in major trials
  - Cytokine Release Syndrome (CRS): 57-93% of patients
  - Neurotoxicity: 39-67%

- Neither CRS nor neurotoxicity were predicted by animal modelling before clinical translation.

Palazzo, L., Pieri, V., Berzero, G., & Filippi, M. (2024). CAR-T Cells for the Treatment of Central Nervous System Tumours: Known and Emerging Neurotoxicities. *Brain sciences*, *14*(12), 1220.

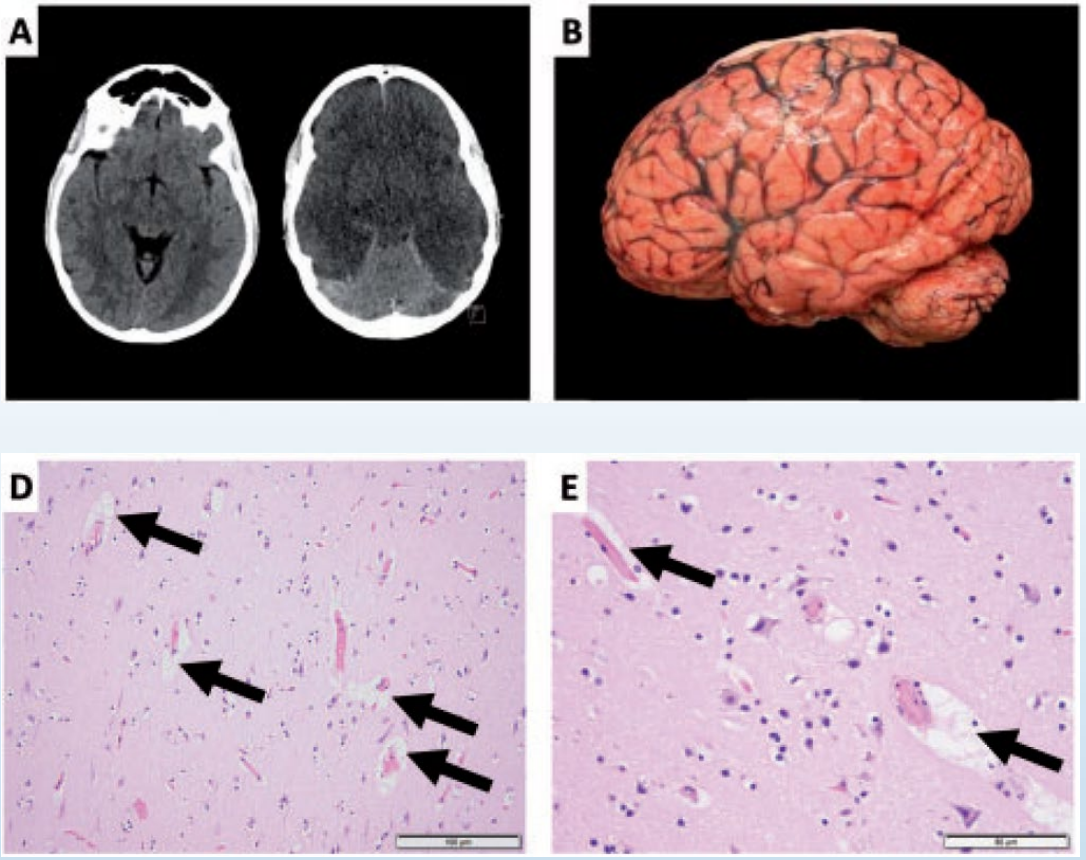
Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)

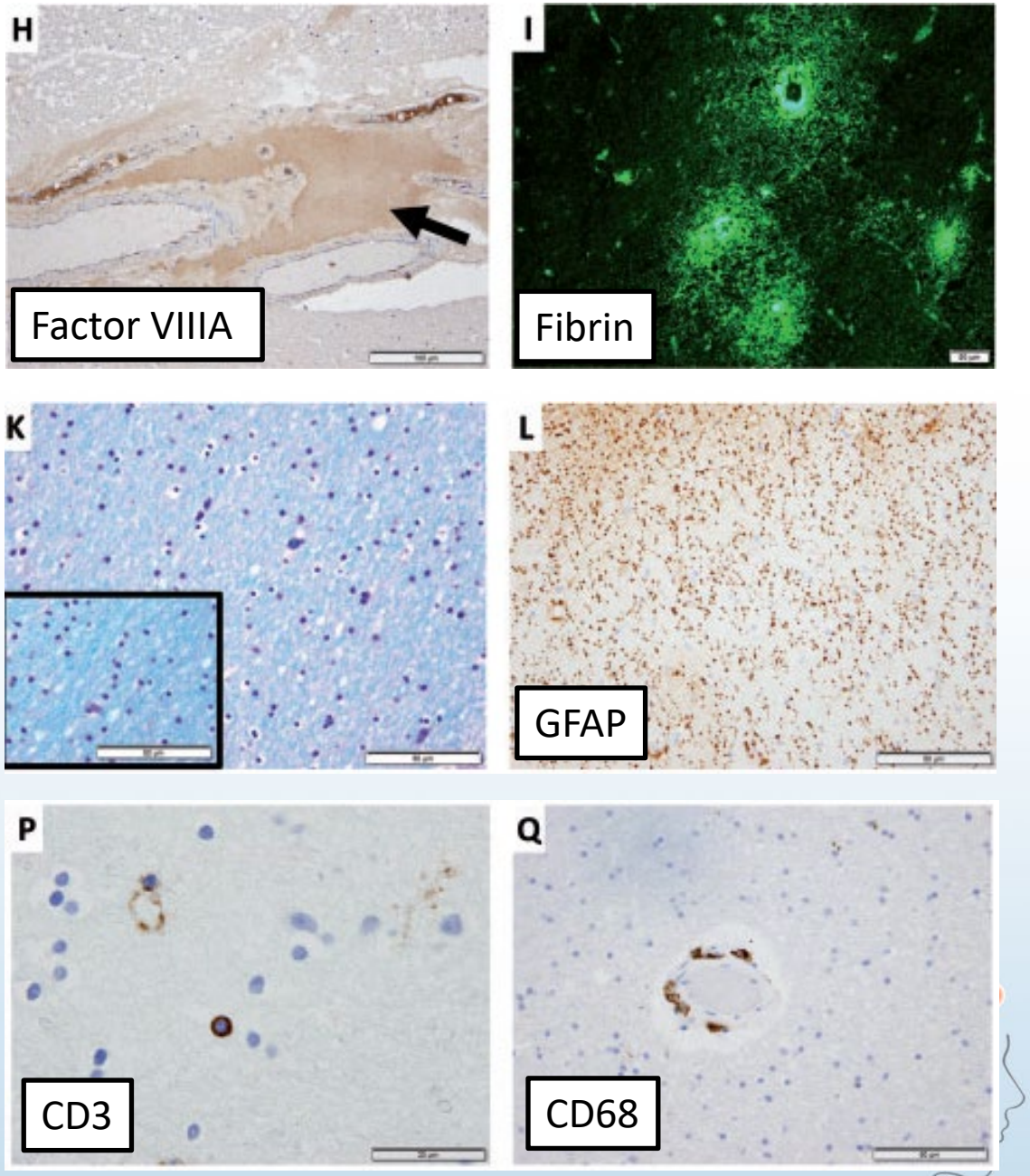
- Stereotyped encephalopathy
  - **Aphasia**, dysgraphia, apraxia, attention deficit, seizures
  - Cerebral edema
- Within days of CAR-T cell infusion
- MRI: focal areas of T2/FLAIR hyperintensity or diffusion restriction; rarely diffuse leptomeningeal enhancement
- Real-world data: 15-30% of patients receiving CD19 CAR-T cells
- Frequently coexists with CRS
- Grade 1 (mild disorientation) to Grade 4 (unarousable).
- Fatal ICANS (Grade 5): 2% of patients receiving CD19 CAR-T cells

Karschnia, P., & Dietrich, J. (2025). Neurological complications of CAR T cell therapy for cancers. *Nature reviews. Neurology*, *21*(8), 422–431

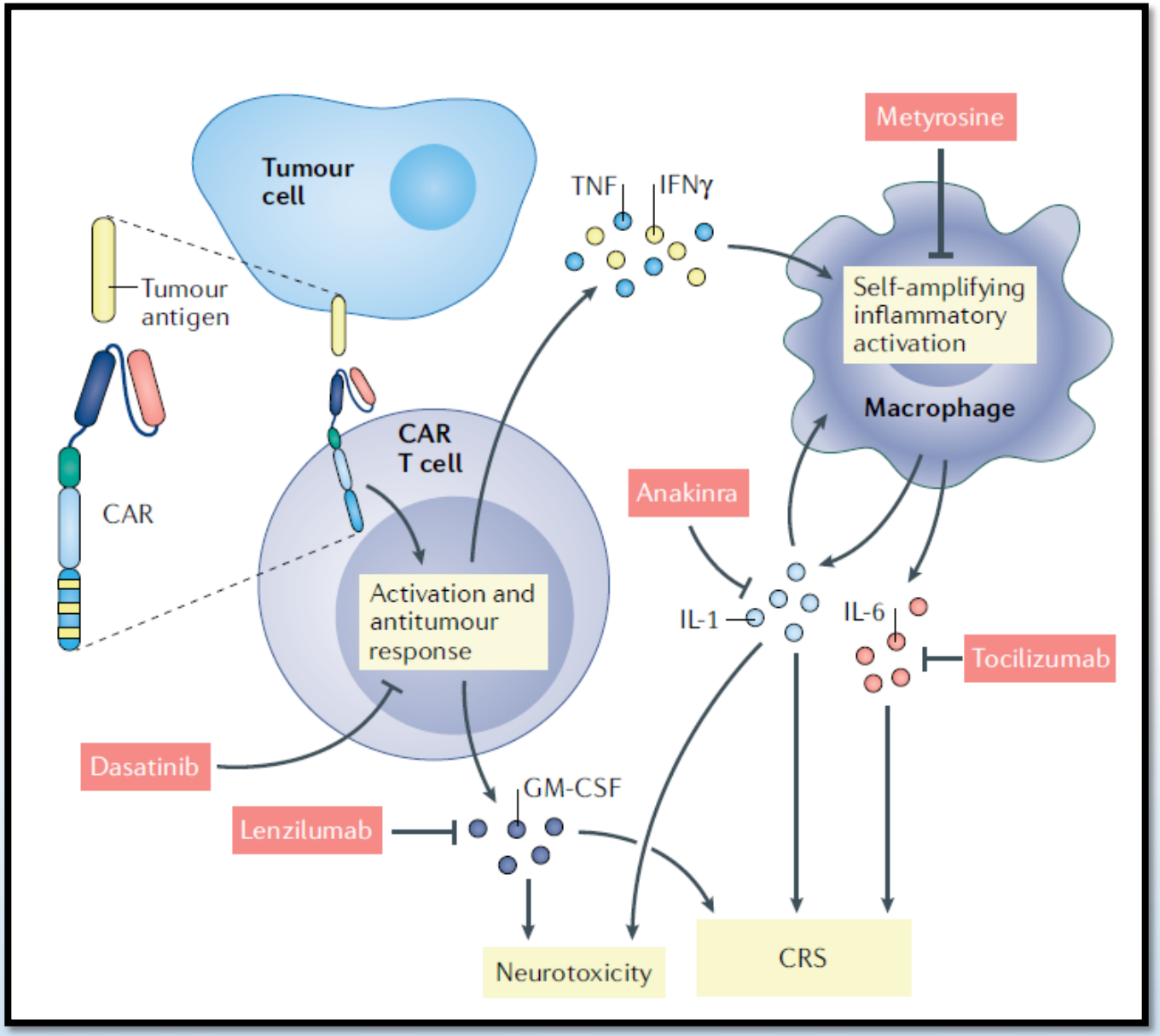
Palazzo L, Pieri V, Berzero G, Filippi M. CAR-T Cells for the Treatment of Central Nervous System Tumours: Known and Emerging Neurotoxicities. Brain Sci. 2024 Nov 30;14(12):1220.

Neuropathology of a Case with Fatal CAR T-cell-Associated Cerebral Edema



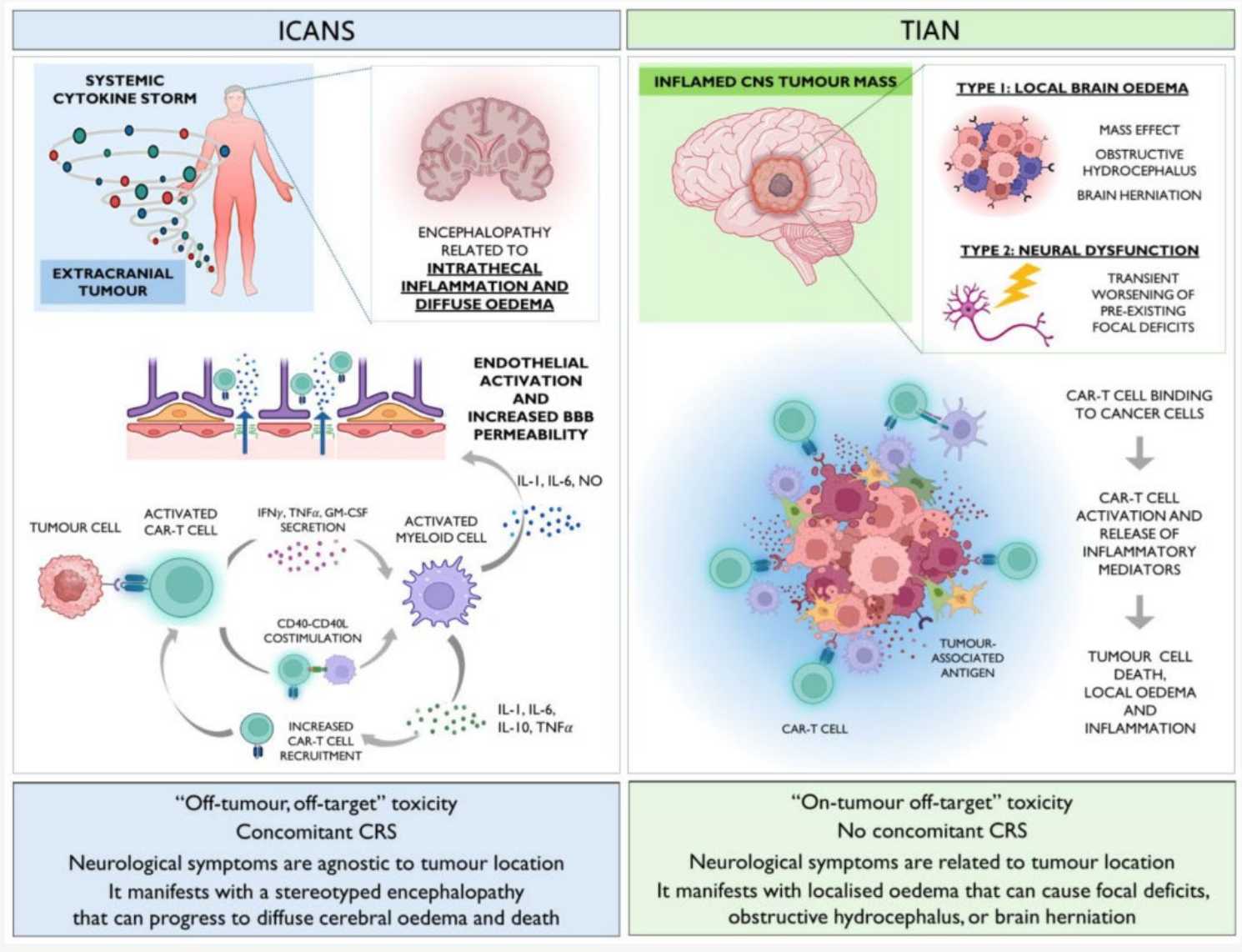


Torre, M., Solomon, I. H., Sutherland, C. L., et al. (2018). Neuropathology of a Case With Fatal CAR T-Cell-Associated Cerebral Edema. *Journal of neuropathology and experimental neurology*, *77*(10), 877–882



Larson, R. C., & Maus, M. V. (2021). Recent advances and discoveries in the mechanisms and functions of CAR T cells. *Nature reviews. Cancer*, *21*(3), 145–161.

Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) and Tumour inflammation-associated neurotoxicity (TIAN)



Palazzo L, Pieri V, Berzero G, Filippi M. CAR-T Cells for the Treatment of Central Nervous System Tumours: Known and Emerging Neurotoxicities. Brain Sci. 2024 Nov 30;14(12):1220.

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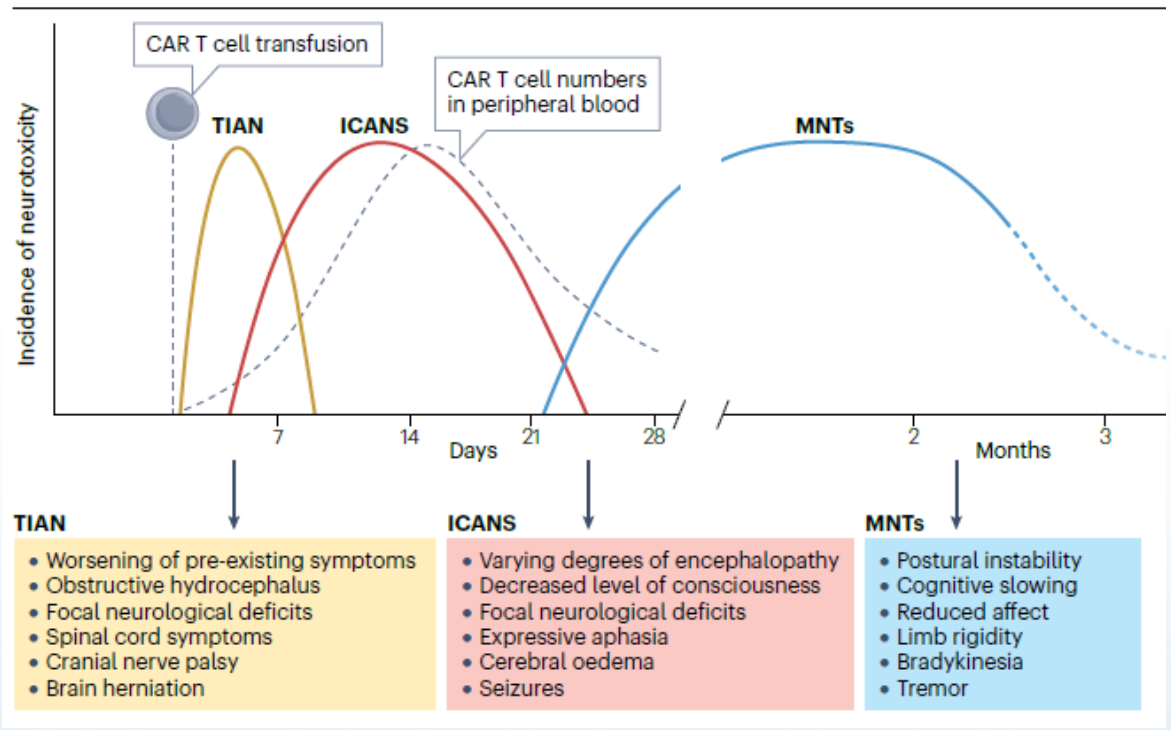
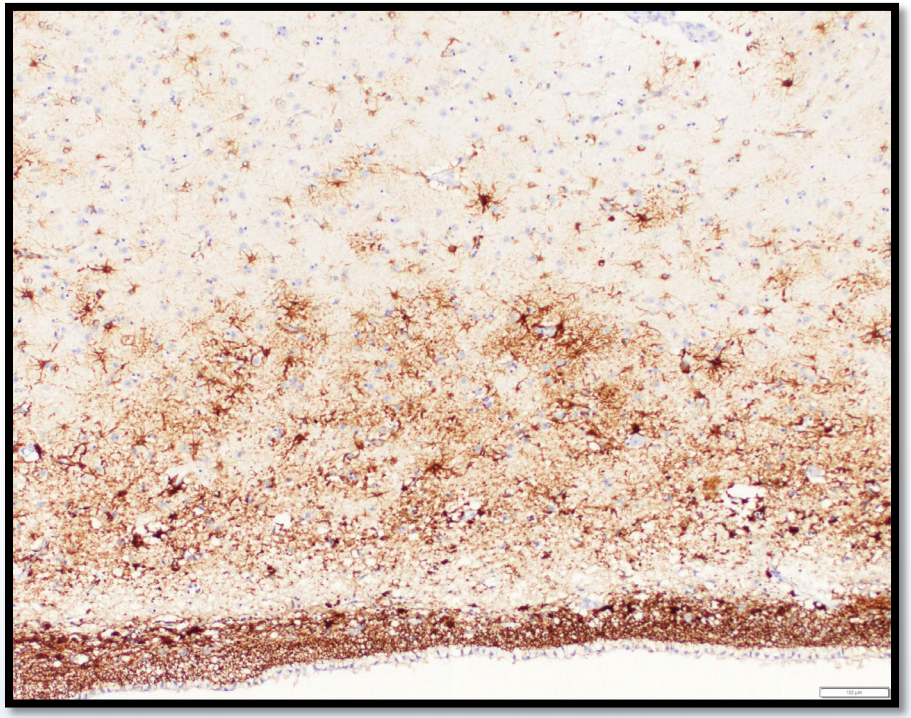
Known and emerging CAR T-related toxicities





BCMA targeted CAR T-cells for treatment of myeloma: 5% of study subjects developed a motor and neurocognitive disorder with limb rigidity, postural instability and tremor, starting weeks to months after infusion.

Potential mechanism: On-target, off-tumor cross reactivity with BCMA expressed at low levels in the striatum

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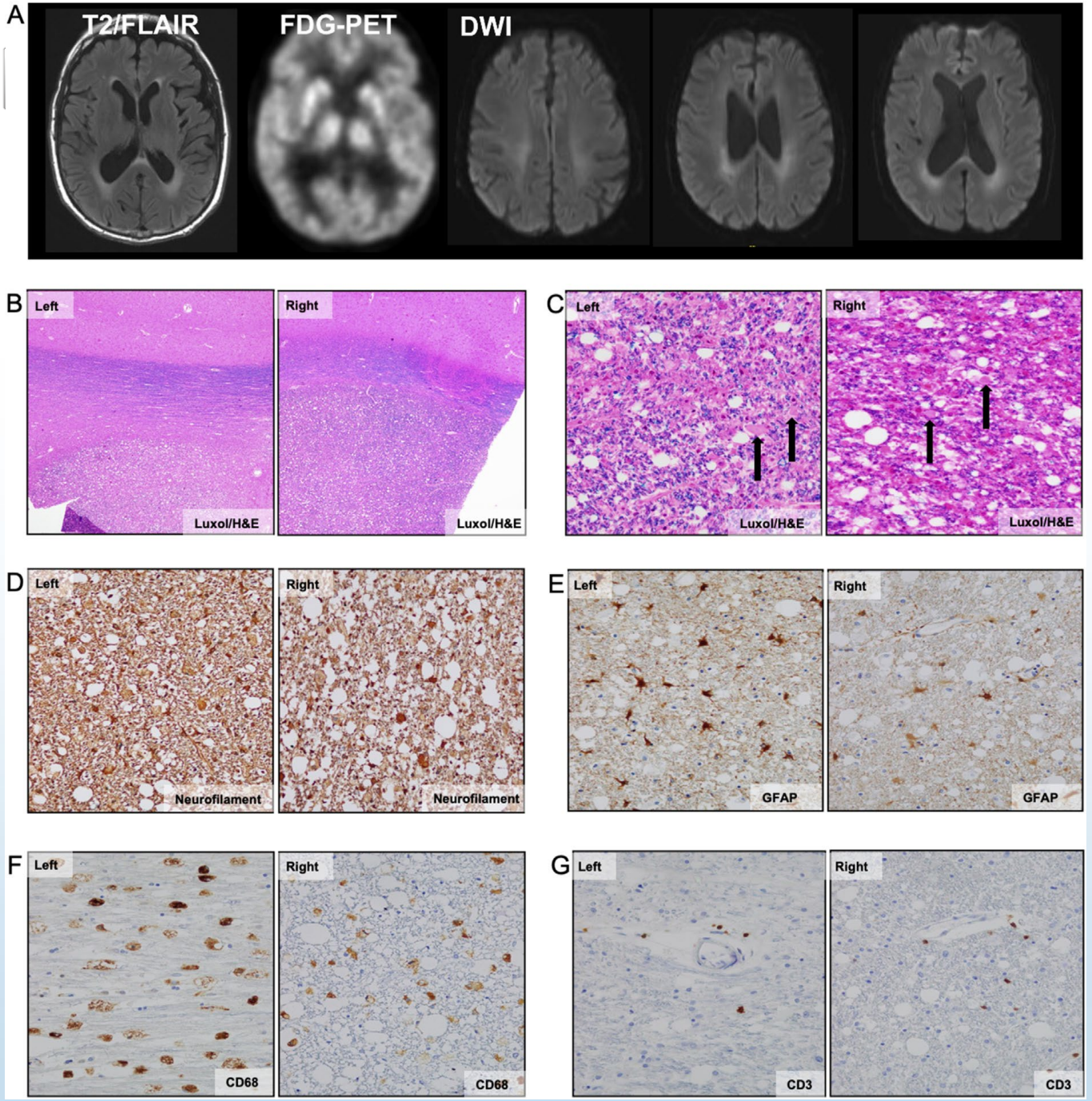
Karschnia, P., & Dietrich, J. (2025). Neurological complications of CAR T cell therapy for cancers. *Nature reviews. Neurology*, *21*(8), 422–431

Fatal neurotoxicity after chimeric antigen receptor T-cell therapy: An unexpected case of fludarabine-associated progressive leukoencephalopathy

A 74-year-old man with a 3-year history of refractory DLBCL after multiple lines of therapy developed progressive neurologic symptoms leading to death several weeks after receiving CD19-targeted CAR-T infusion (following lymphodepleting chemotherapy with fludarabine/cyclophosphamide).

Bilateral white matter injury with geographic regions of disruption, vacuolization, and abundant axonal spheroids. Abundant macrophages and rare CD3-positive T-cells were present.

Temporal correlation does not equal causation!



Winter SF, Martinez-Lage M, Clement NF, et al. Eur J Cancer. 2021 Feb;144:178-181.

THANK YOU!

After a question about nano/microplastics during the live session on 8.27, Dr. Beatriz Lopes shared this reference:

Nihart, A. J., Garcia, M. A., El Hayek, E., Liu, R., Olewine, M., Kingston, J. D., Castillo, E. F., Gullapalli, R. R., Howard, T., Bleske, B., Scott, J., Gonzalez-Estrella, J., Gross, J. M., Spilde, M., Adolphi, N. L., Gallego, D. F., Jarrell, H. S., Dvorscak, G., Zuluaga-Ruiz, M. E., West, A. B., … Campen, M. J. (2025). Bioaccumulation of microplastics in decedent human brains. *Nature medicine*, *31*(4), 1114–1119.