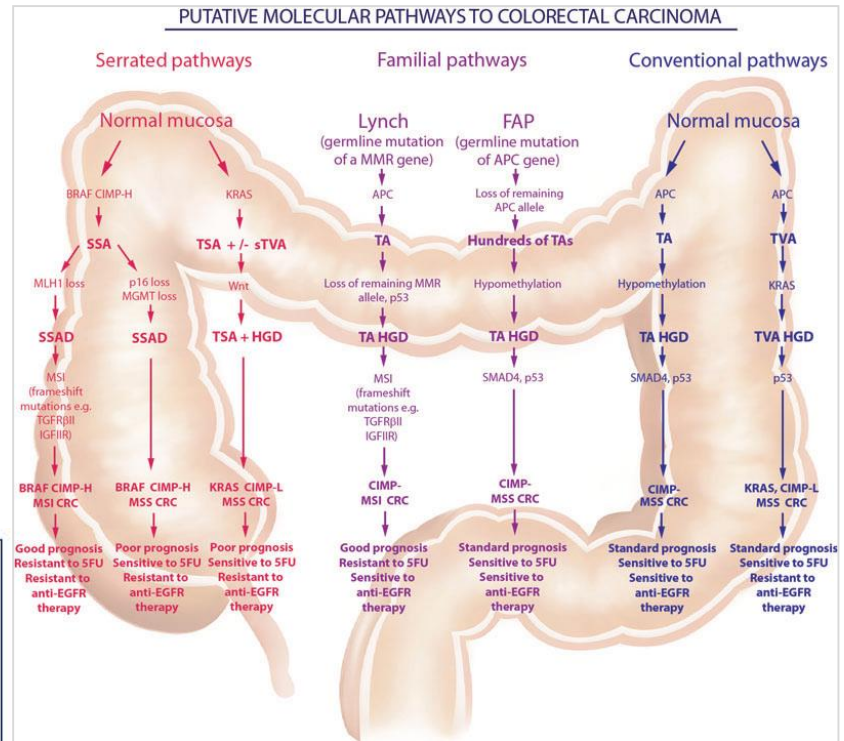
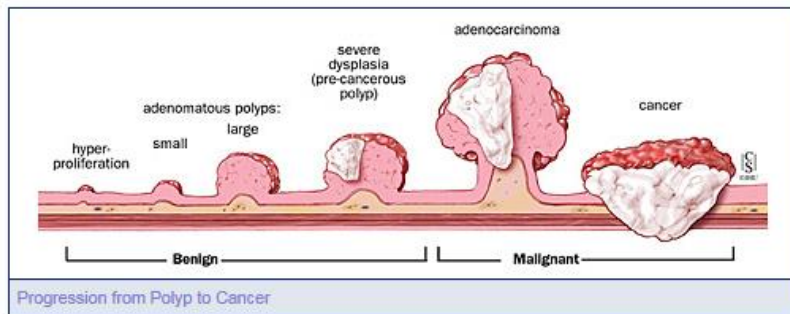
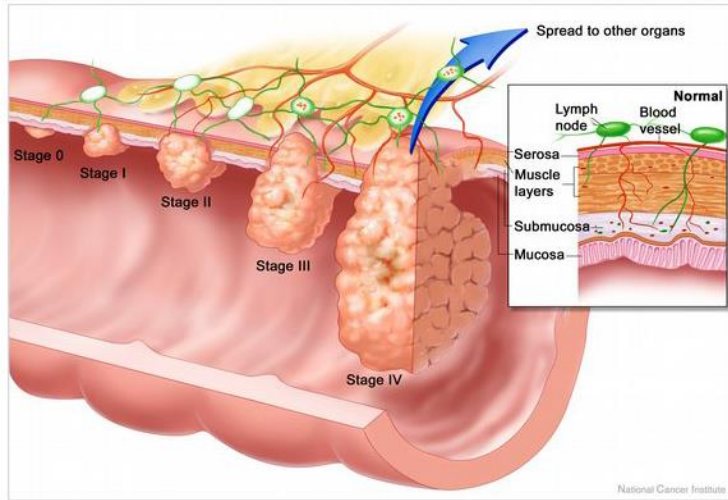




## Primary CNS lymphoma and so called “prelymphomatous” conditions

Caterina Giannini MD PhD  
Professor of Laboratory Med/Pathology & Neurosurgery  
Mayo Clinic, Rochester, MN

# There are not prelymphomatous conditions in the brain



## The Progression from Polyp to Cancer

## In the brain

- Lymphoma can disguise itself as a variety of other conditions
- A variety of conditions, which are not lymphoma, either clinically &/or by imaging prompt consideration of lymphoma



# Primary CNS lymphoma: a mimicker and a dissimulator

Caterina Giannini MD PhD  
Professor of Laboratory Med/Pathology & Neurosurgery  
Mayo Clinic, Rochester, MN

# CNS lymphoma: objectives

- Discuss Primary CNS lymphoma
- Lymphoma in disguise:
  - Vanishing Lymphoma
  - Sentinel lesions
- Immunodeficiency/EBV associated lymphoma
  - Lymphomatoid Granulomatosis
- Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)

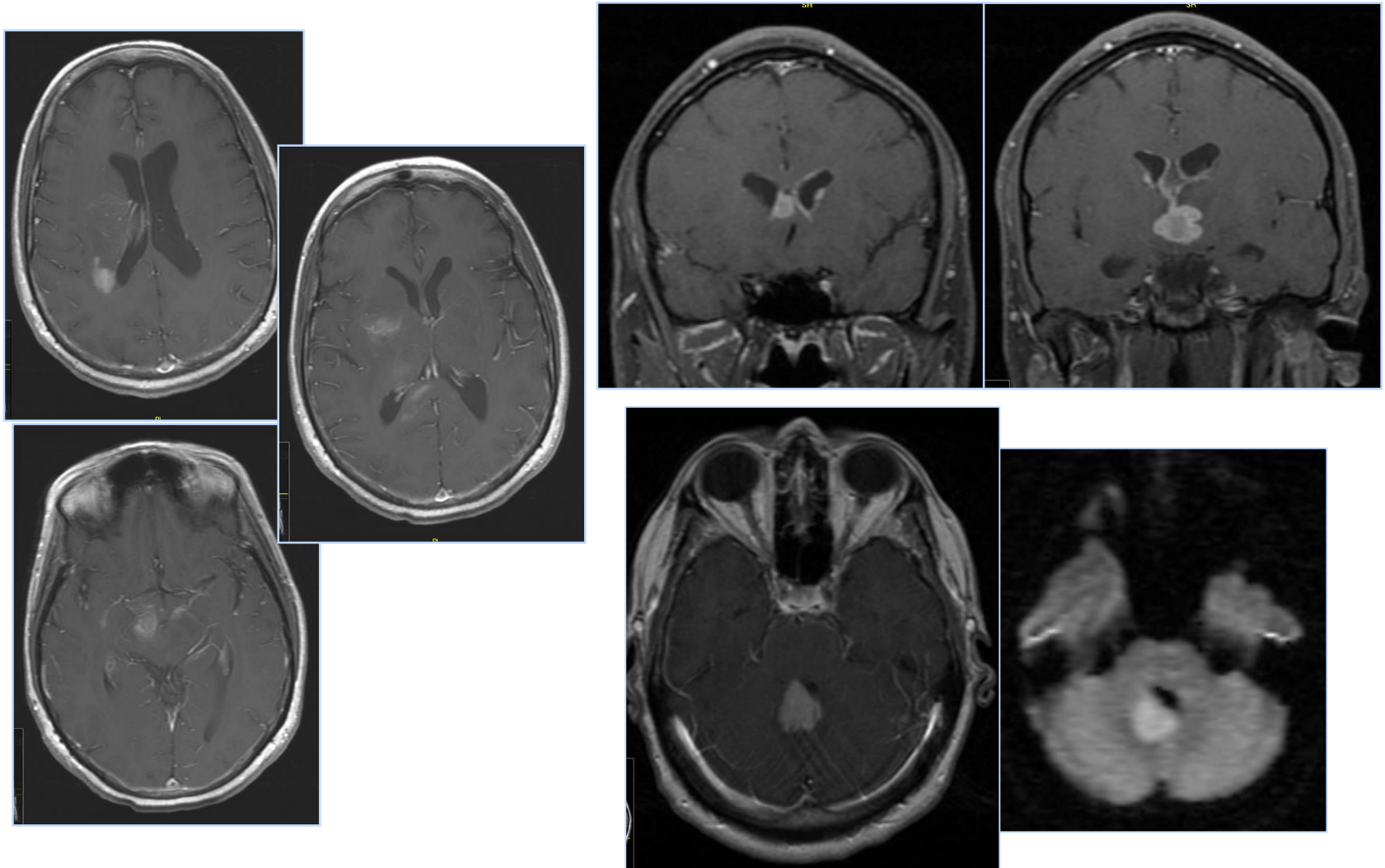
# Primary CNS Lymphoma

- WHO (2008) definition
  - Primary diffuse large B-cell lymphoma
  - Confined to the CNS and/or eye
  - Immunocompetent patients
- All ages, peak 6-7<sup>th</sup> decade M:F ratio 3:2
- Rare: incidence 5/10<sup>6</sup>/year, but increasing
  - <1% of all NHL
  - $\pm$  2% of all brain tumors
- Aggressive lymphoma, with dismal prognosis

# Primary CNS Lymphoma

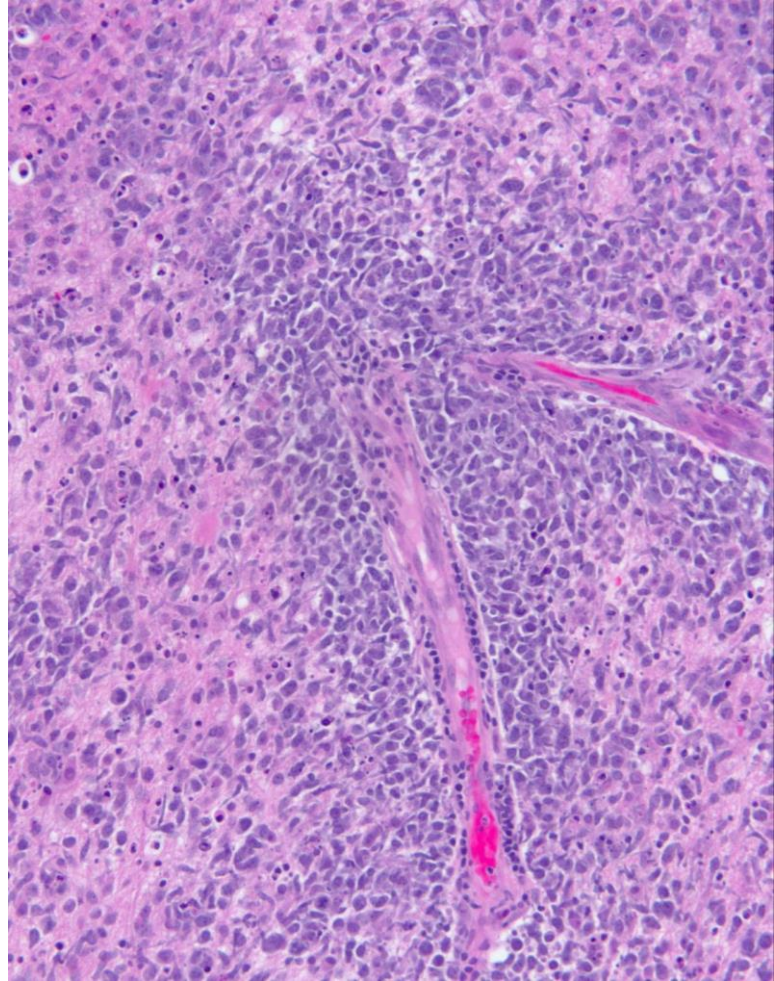
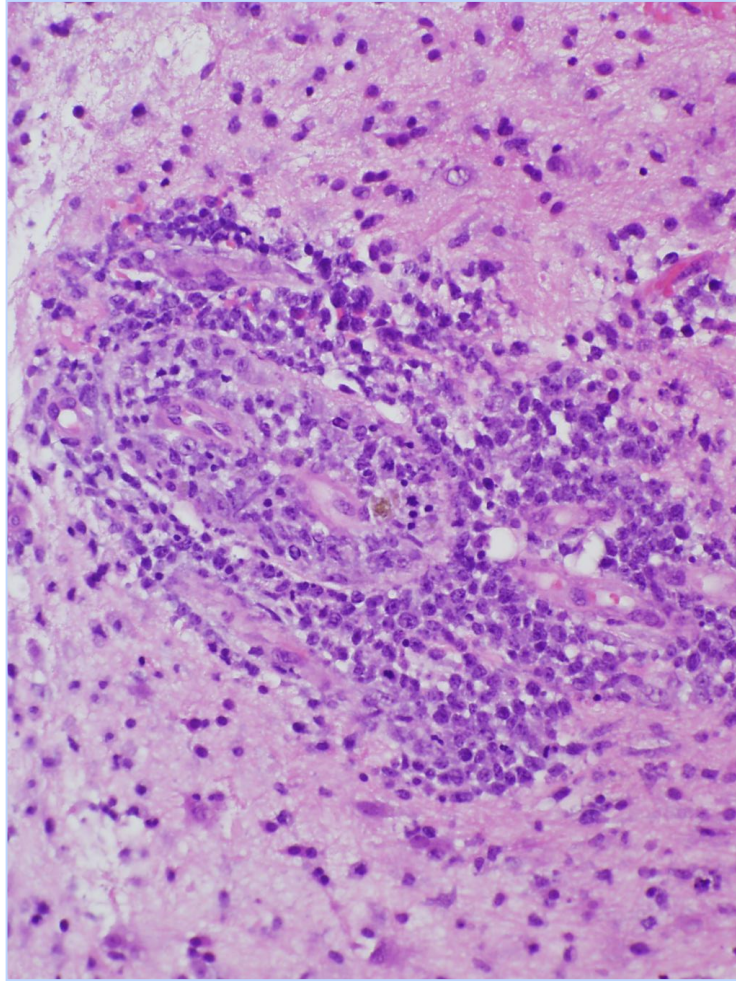
- 50-80% focal neurologic deficits
- Supratentorial (60%), posterior fossa (13%), primary leptomeningeal (8%)
- Neuroimaging quite suggestive:
  - Location: deep, periventricular, symmetric subependymal
  - MRI signal: T2 iso-hyperintense; diffusion restriction; densely enhancing post-contrast; limited peritumoral edema

# Primary CNS Lymphoma: Imaging

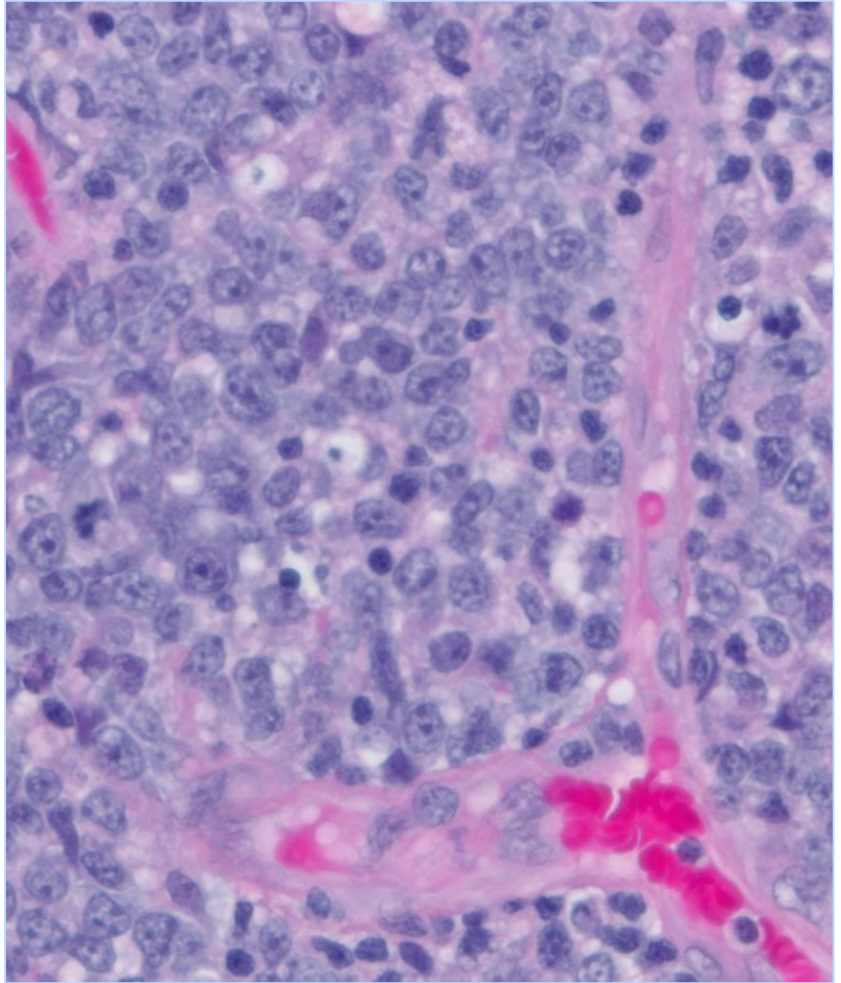
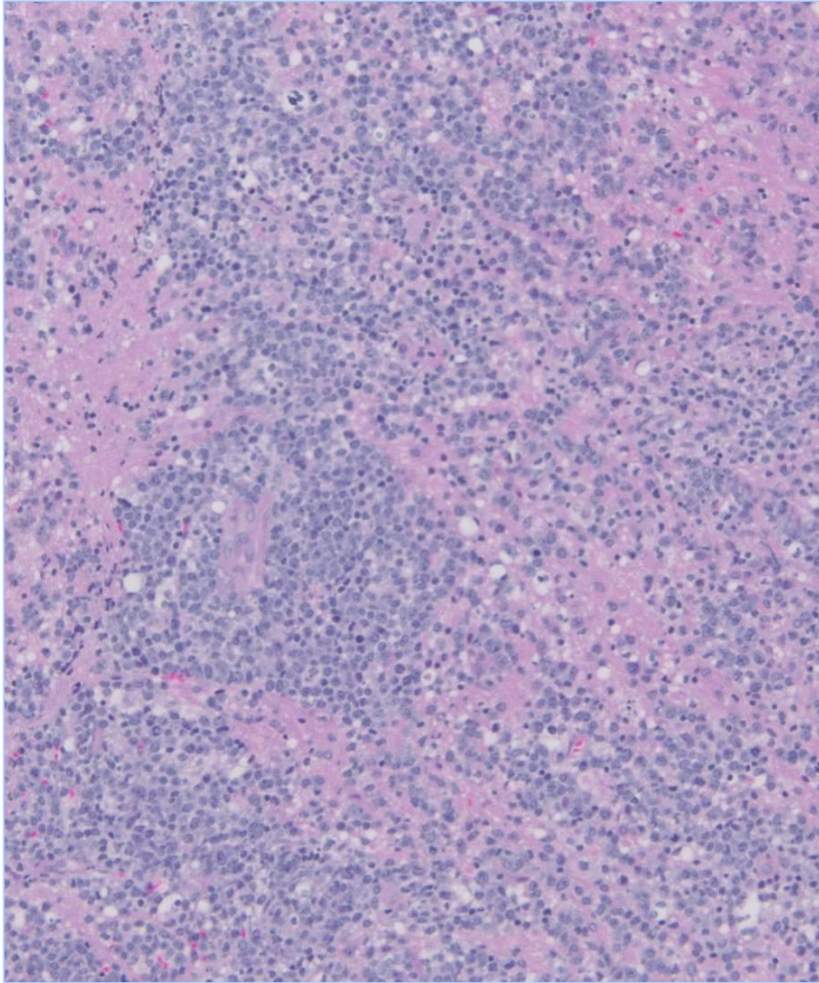


# Primary CNS Lymphoma

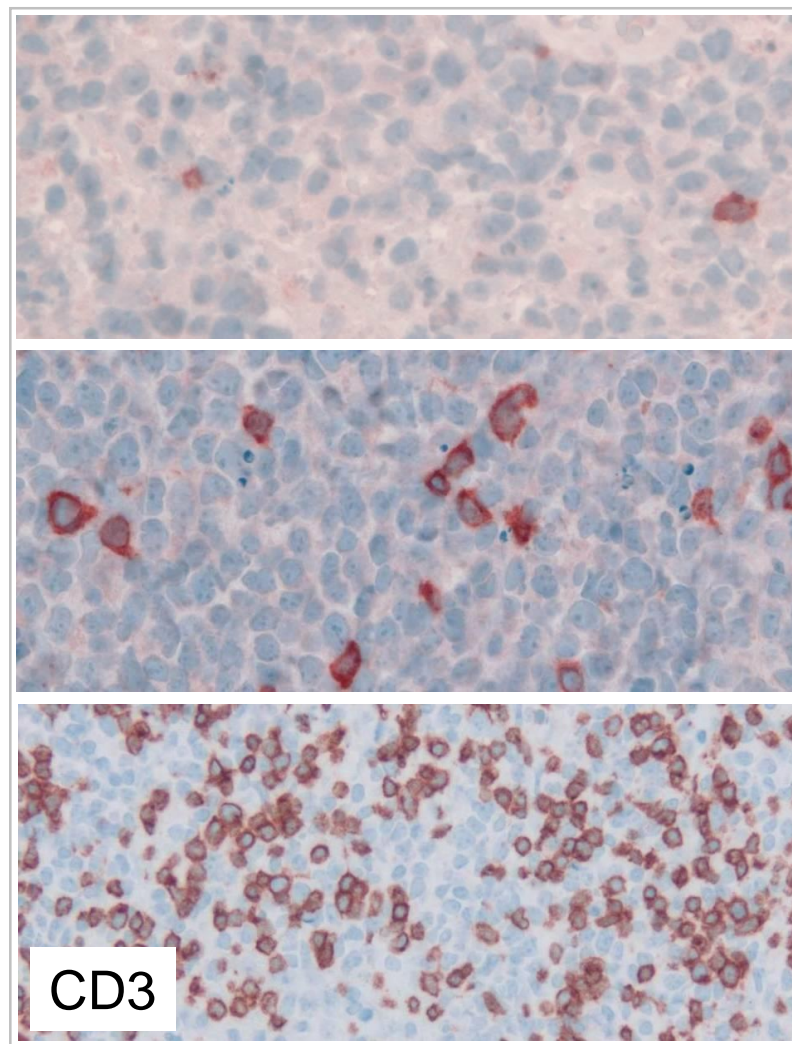
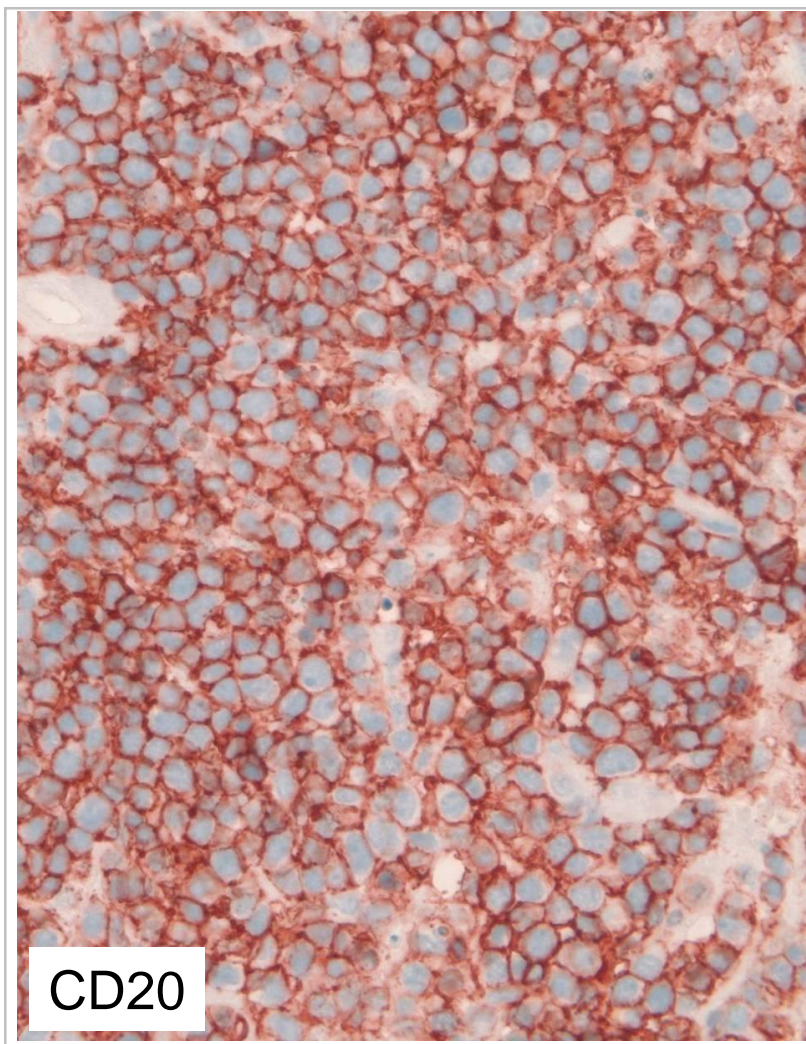
## Perivascular Accumulation of Cells



# Primary CNS Lymphoma

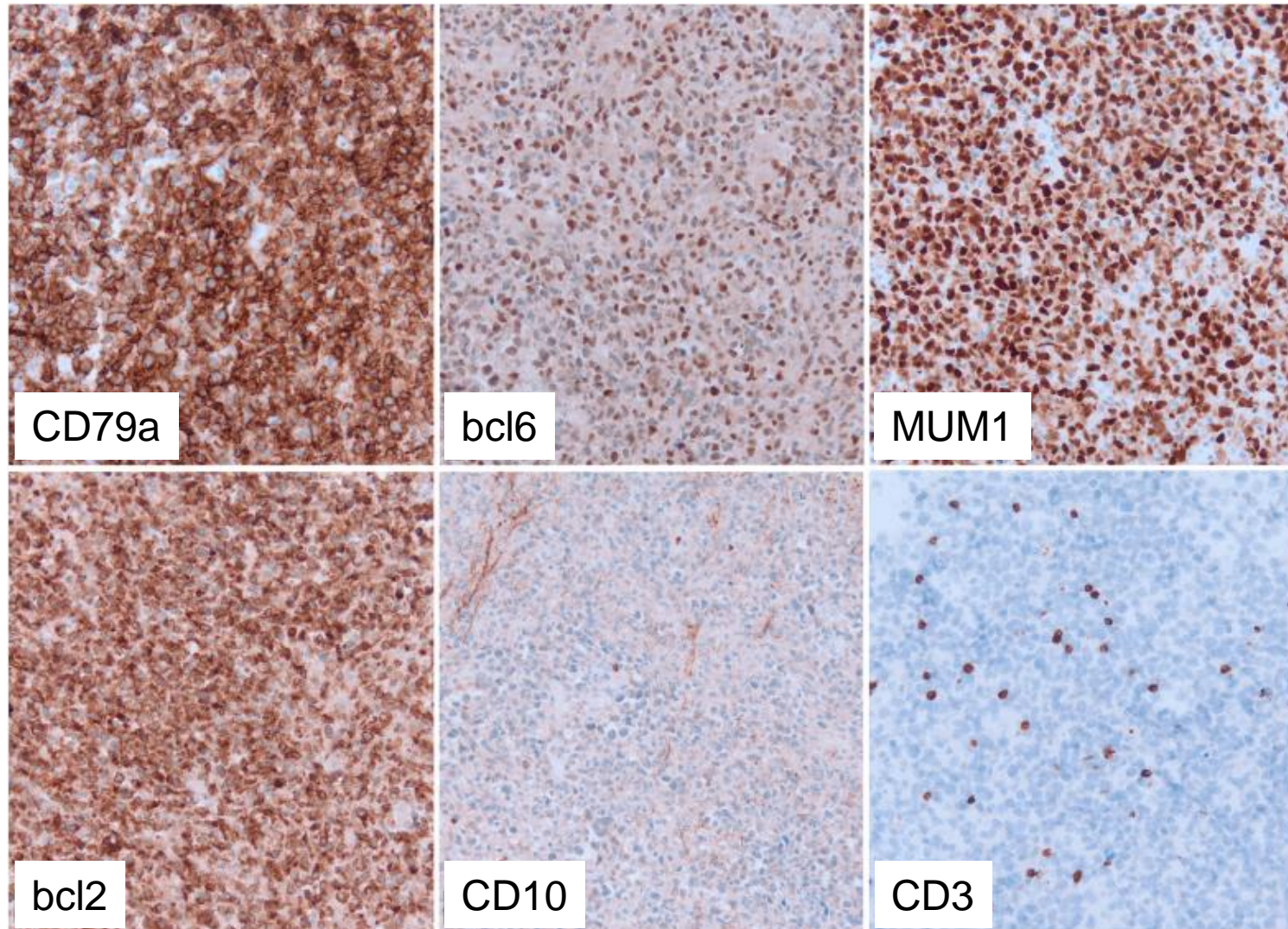


# B-cell Immunophenotype:



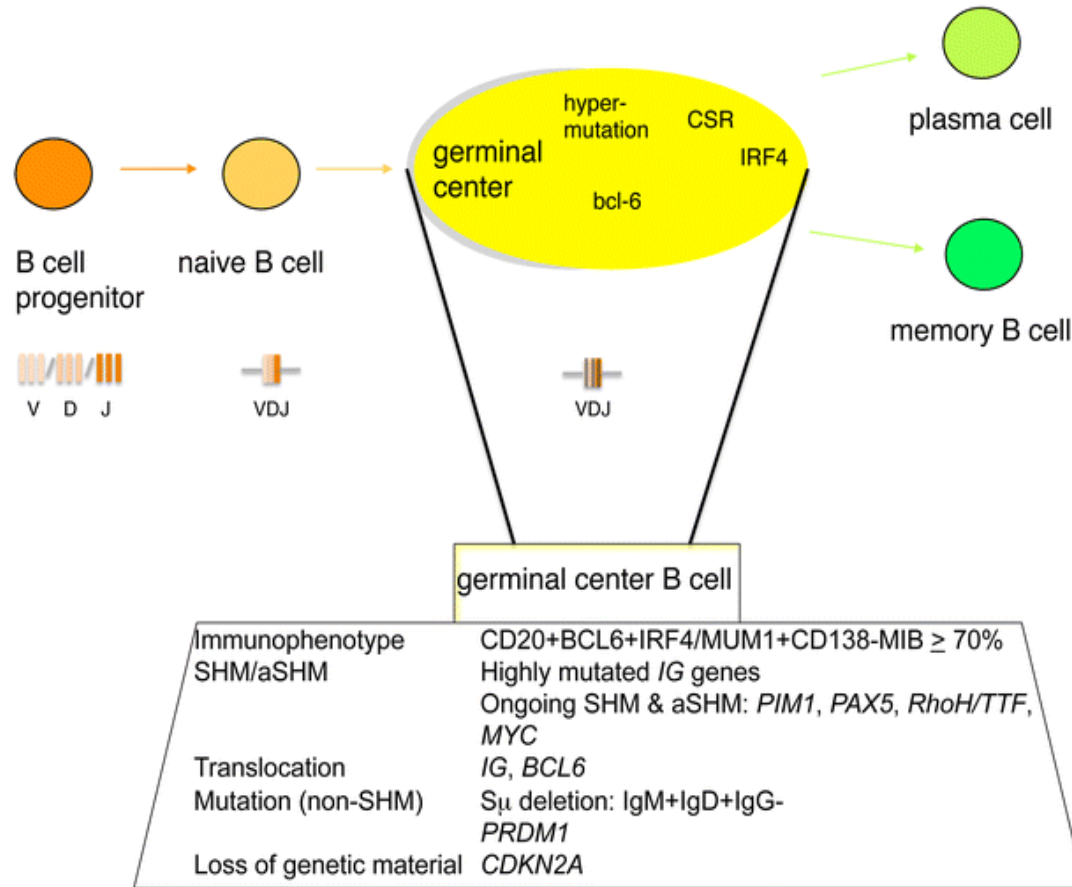
Also CD19, CD79a positive

# PCNSL immunophenotype



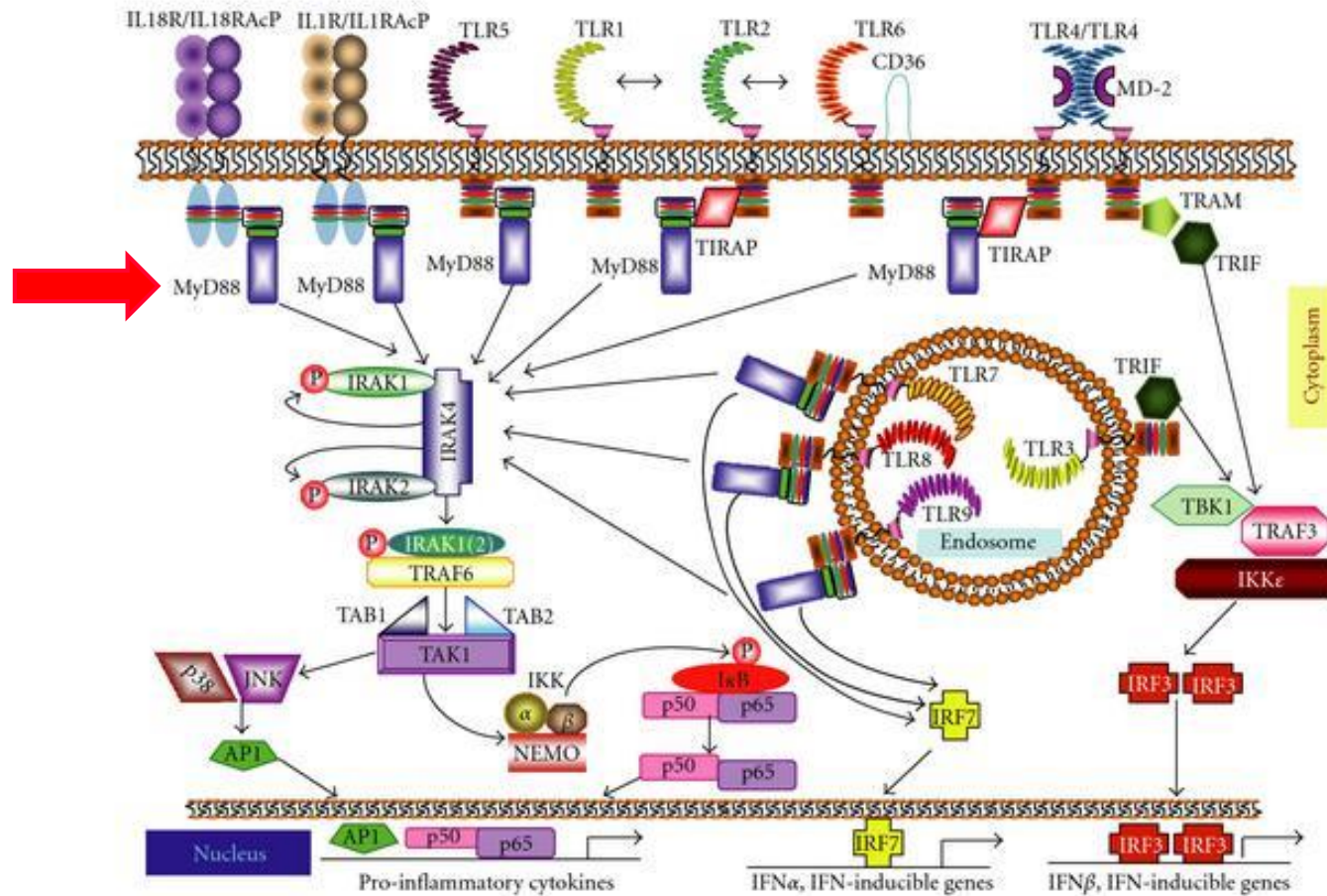
PCNSL is a “unique lymphoma”

# PCNSL histogenetic origin: late GC exit B cell

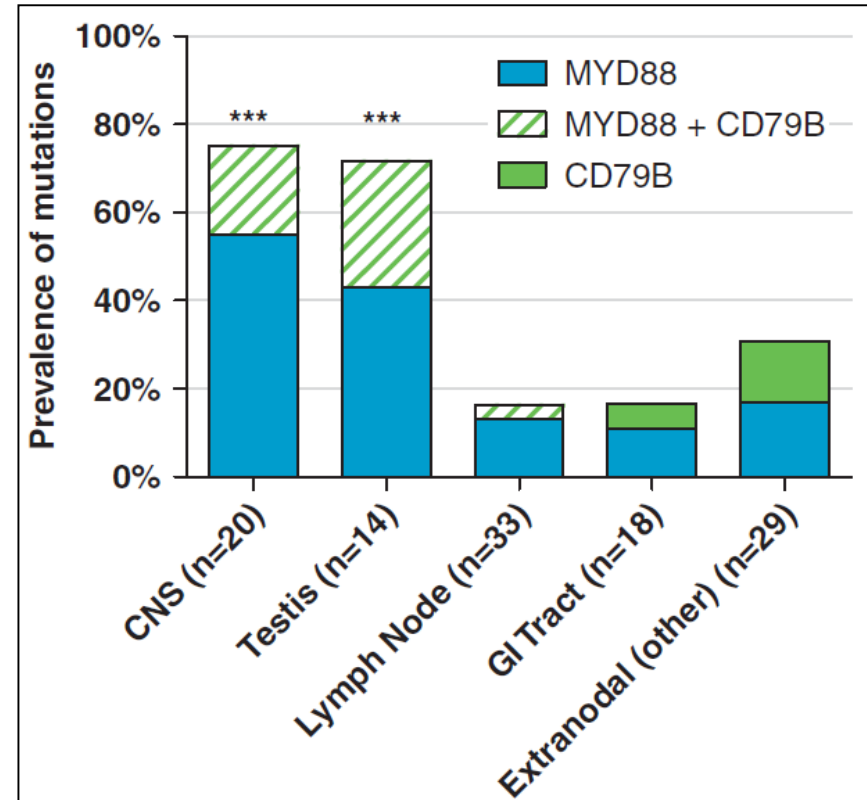
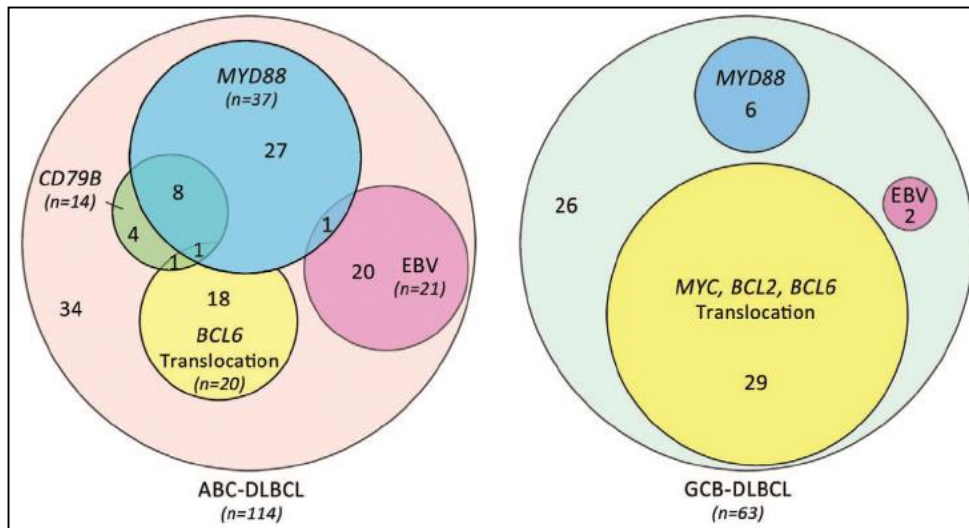


- Gene expression profile suggests they may be related to memory B cells

# MYD88 – Essential Adaptor in Innate Immunity



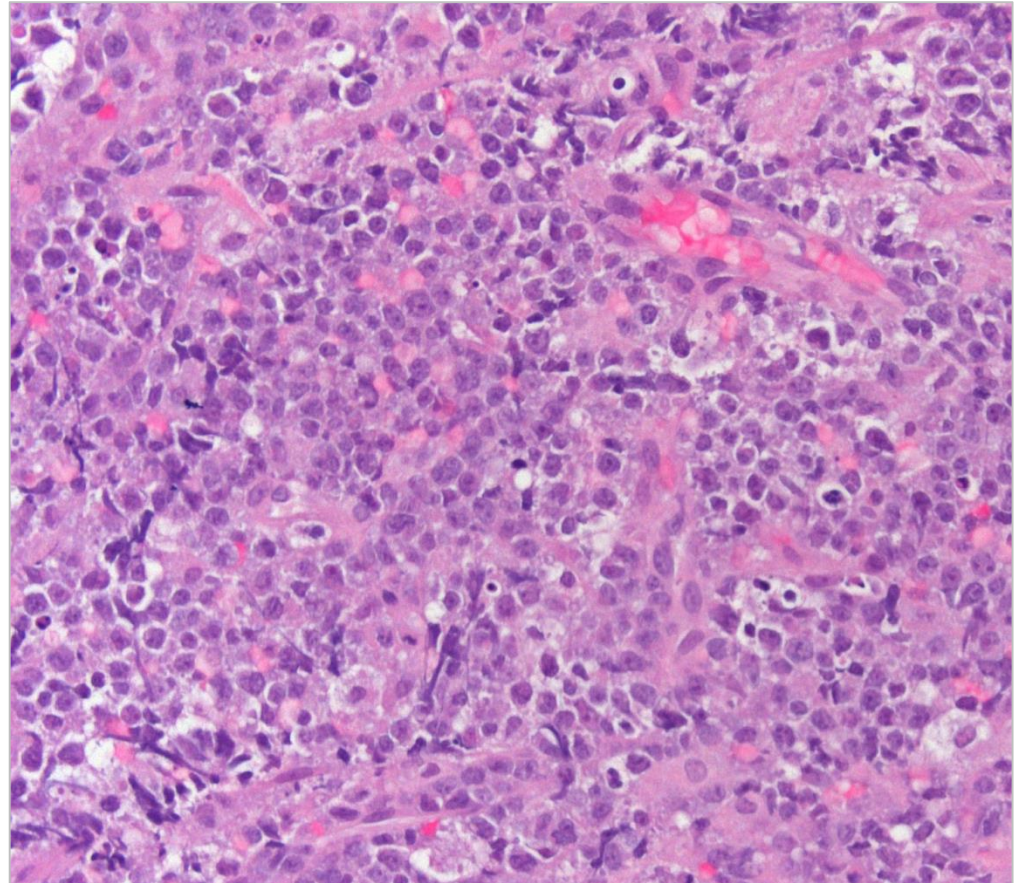
# MYD88 L265P activating mutation, an Emerging Therapeutic Target



Kraan et al. Blood Cancer J(2013)Sep6;3:e139

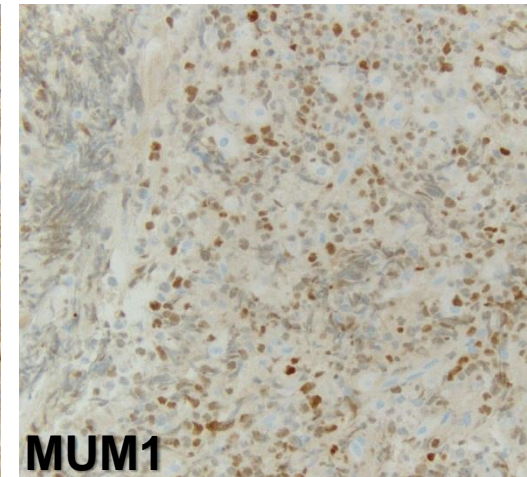
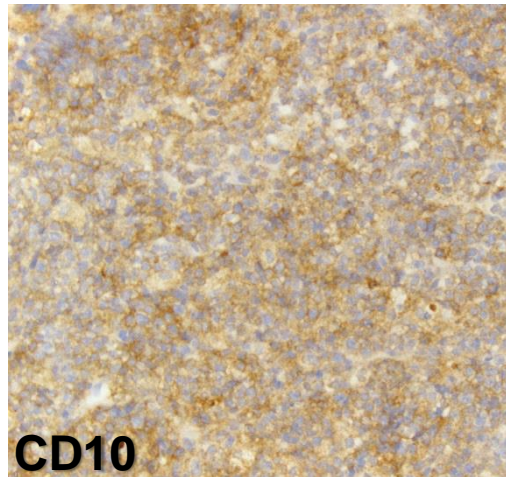
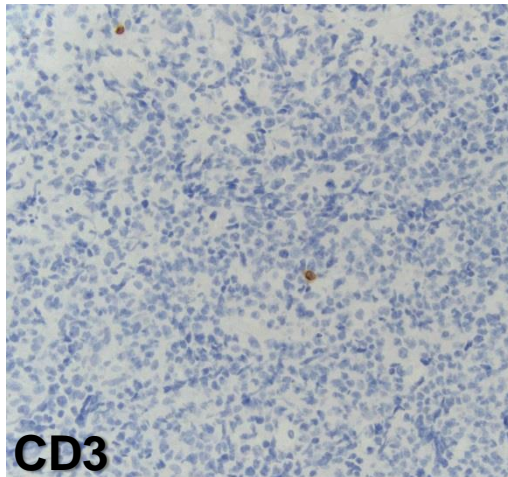
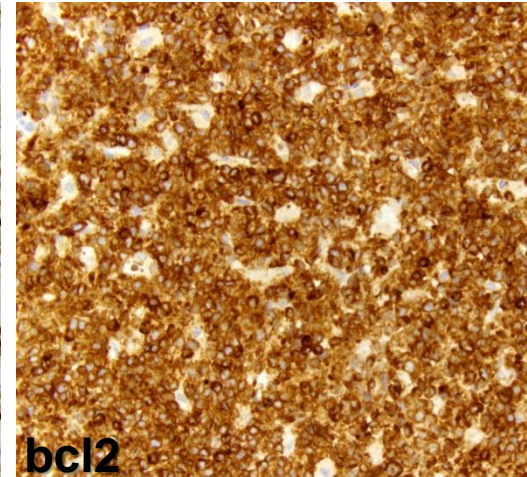
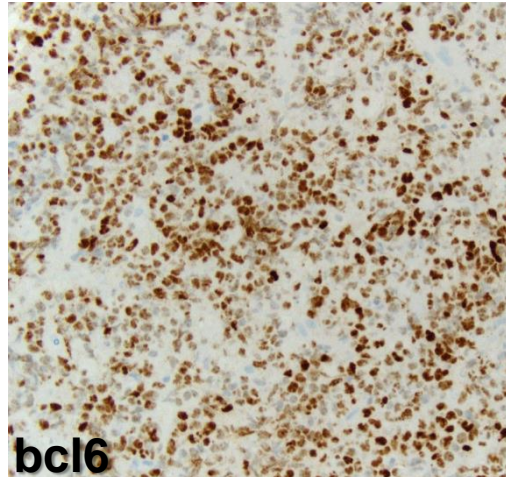
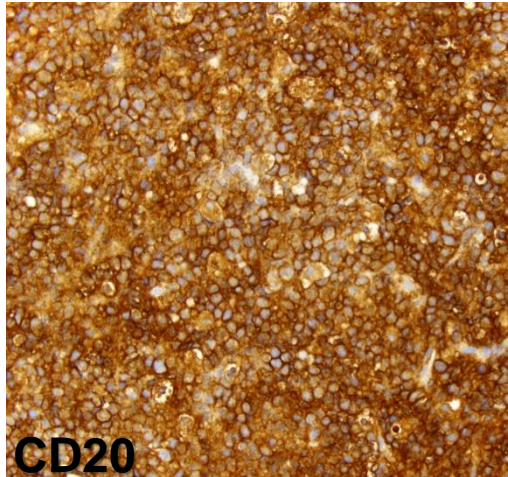
# Recent Case

- 55-year-old man
- Seven months earlier: diagnosed with follicular lymphoma grade 1-2 (axillary node)
- Presents with confusion
- Left frontal enhancing mass
- Brain biopsy



Large Cell Lymphoma

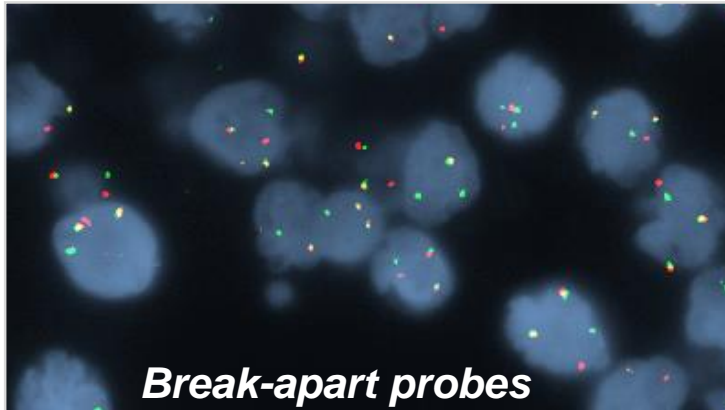
# Follicular Lymphoma with progression or New PCNSL?



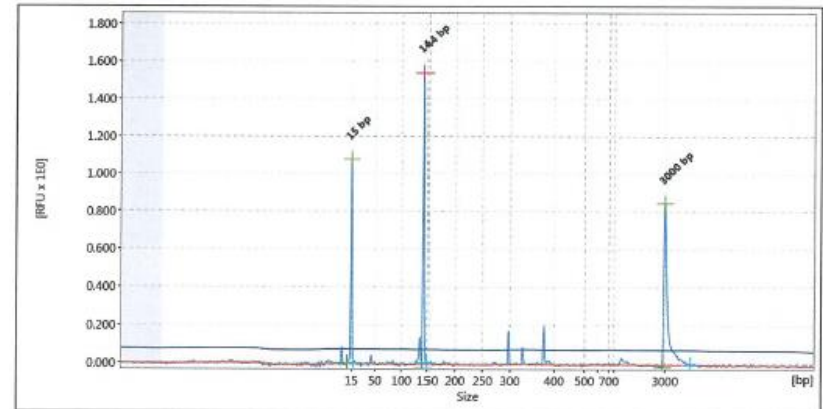
Large B-cell Lymphoma, follicular center phenotype (Hans Algorithm):  
Positive for BCL2 rearrangement (90% of nuclei); No MYD88 mutation

Case

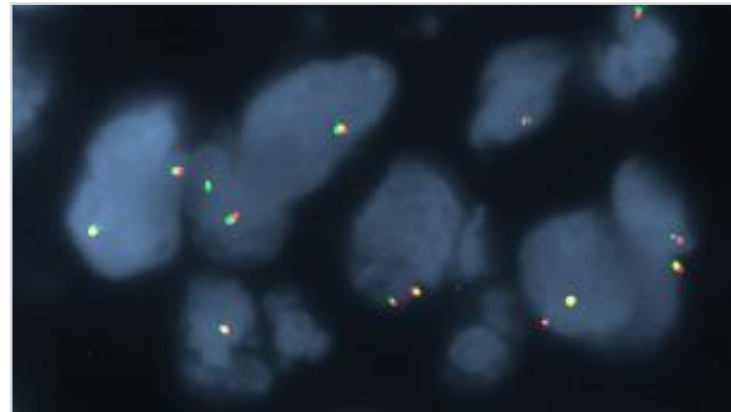
**BCL2 gene rearrangement**



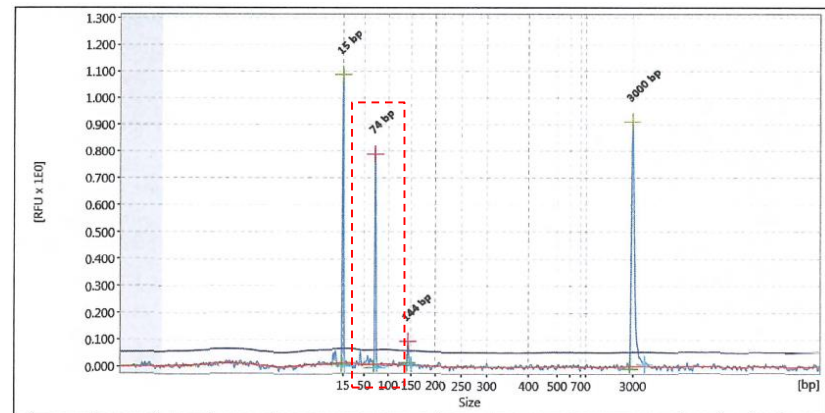
**MYD88**



Control



**Negative Control: no separation**



**Positive Control**

# Lymphoma in disguise: Vanishing Lymphoma

# “Vanishing Lesions”

- Corticosteroids are frequently used to reduce edema and improve symptoms and signs in patients with intracranial mass lesions
- Occasionally, in addition to symptom improvement, the mass lesion becomes smaller/disappears in a few days or weeks, resulting in deferral of biopsy or aspecific pathologic findings
- Presumptive diagnosis is usually lymphoma

# “Steroid” effect

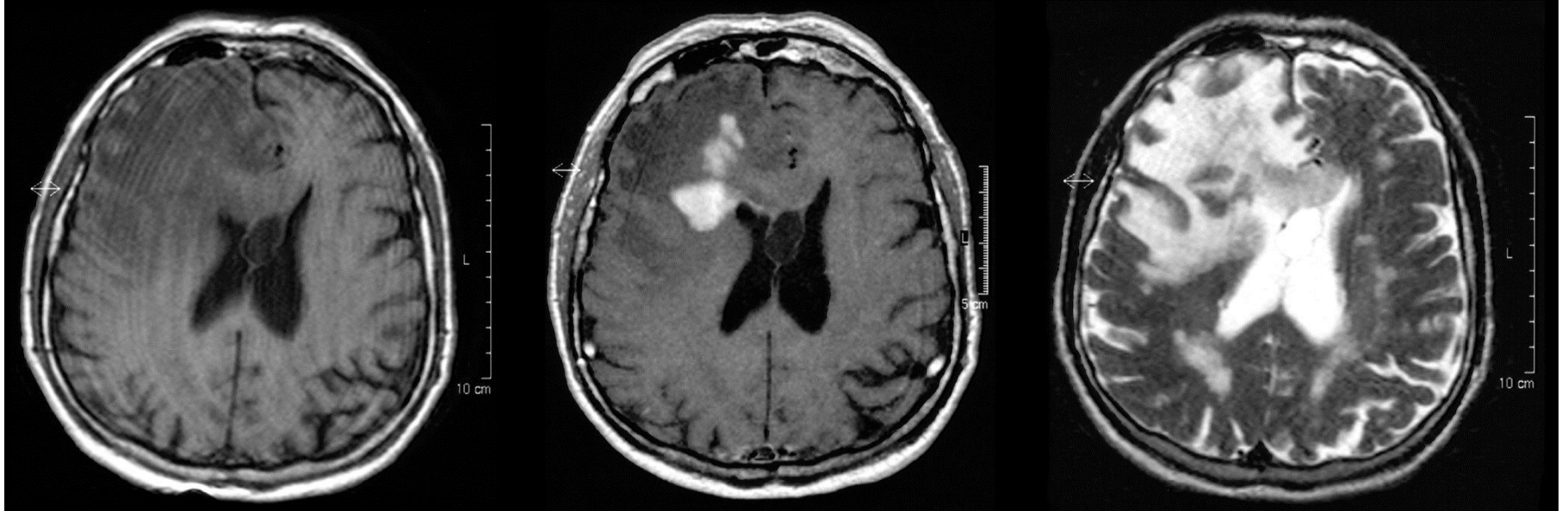
## Glucocorticoid Receptor–Like Antigen in Lymphoma Cell Membranes: Correlation to Cell Lysis

BAHIRU GAMETCHU

*S-49 mouse lymphoma cells undergo lysis when treated with glucocorticoids; the mechanism of this effect is not understood..... suggests that the lysis response of cells to glucocorticoids is mediated by a glucocorticoid receptor-like molecule located in the plasma membrane.*

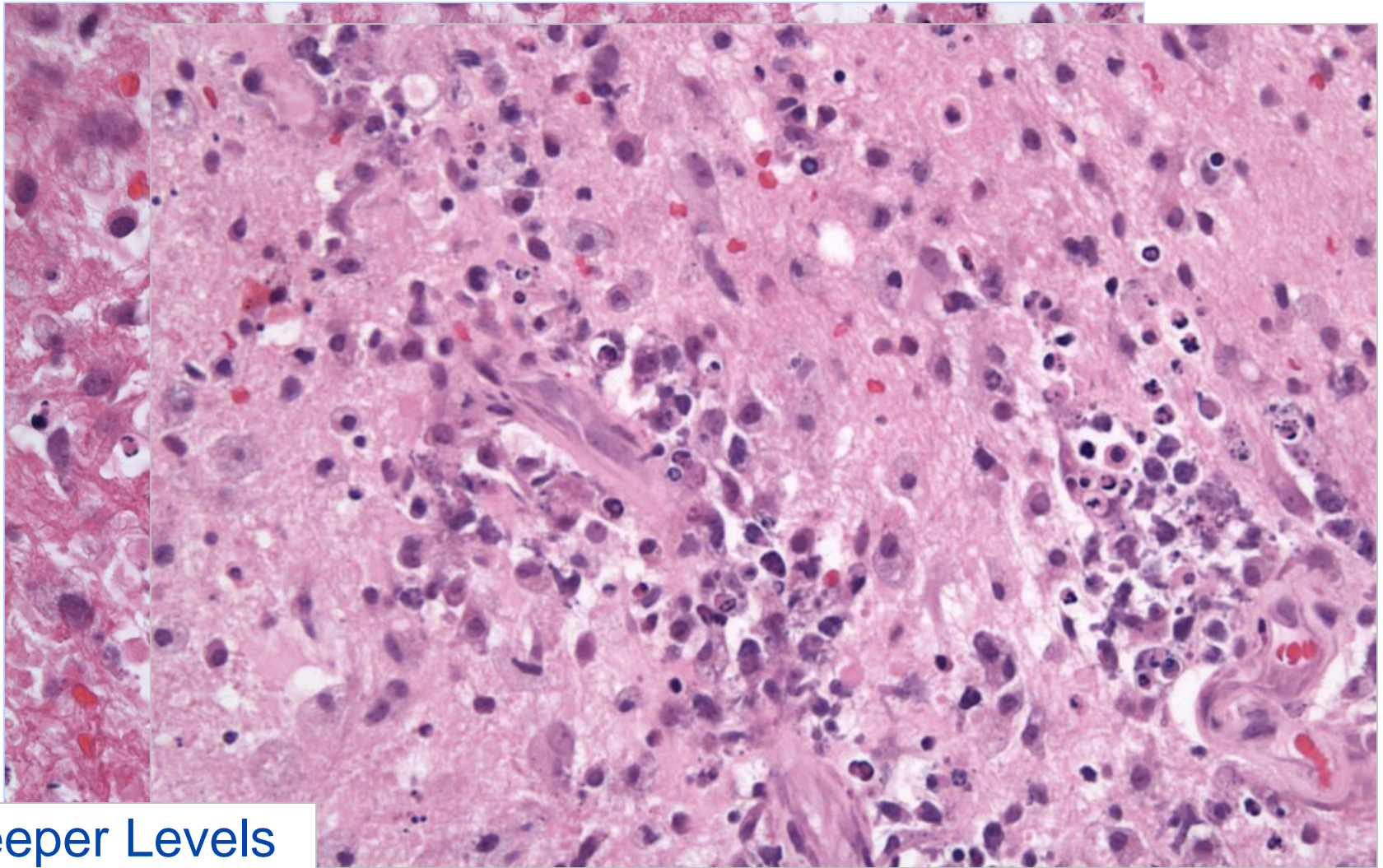
Science 1987;236:456-61

# PCNSL with Steroids effect “Vanishing Lymphoma”



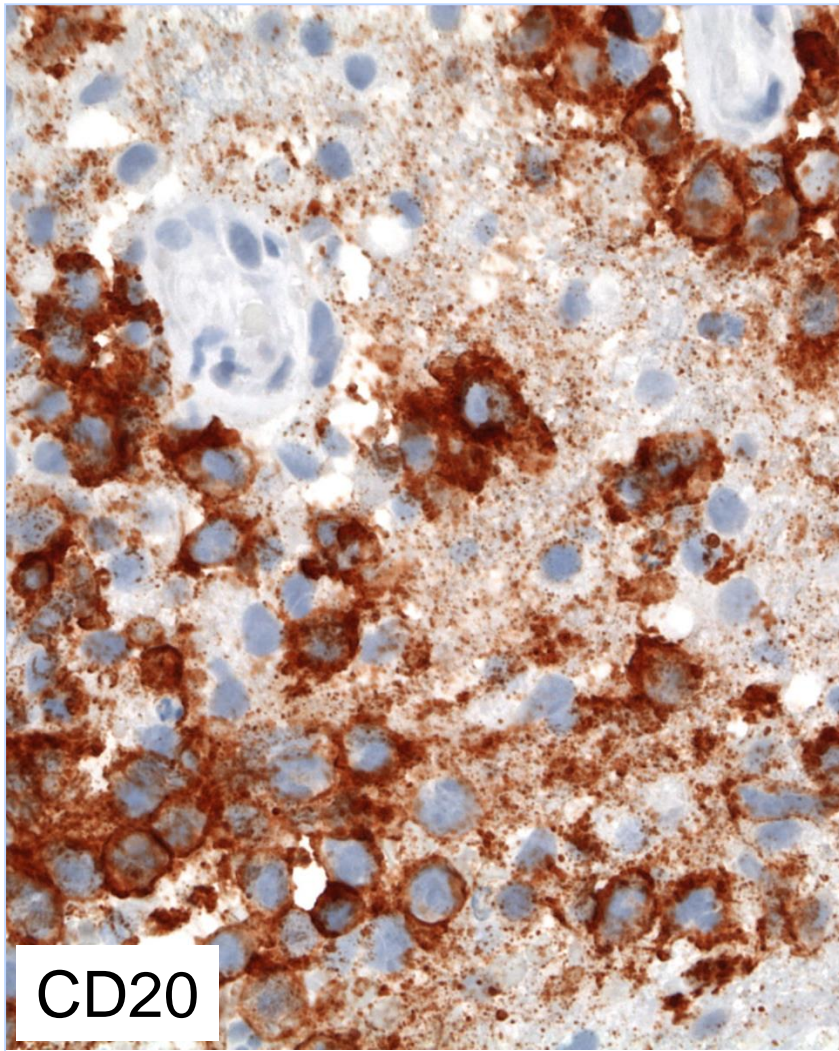
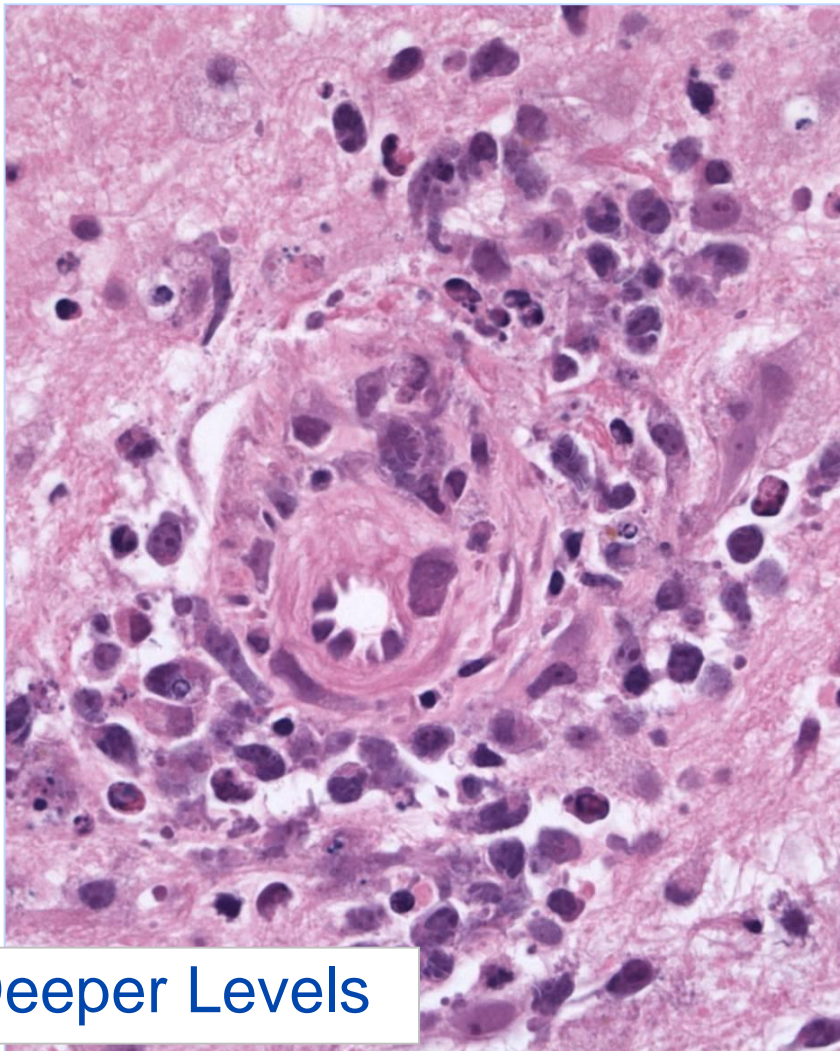
- 81 year-old man
- 24-48 hours of steroids prior to biopsy

# PCNSL with Steroid Effect

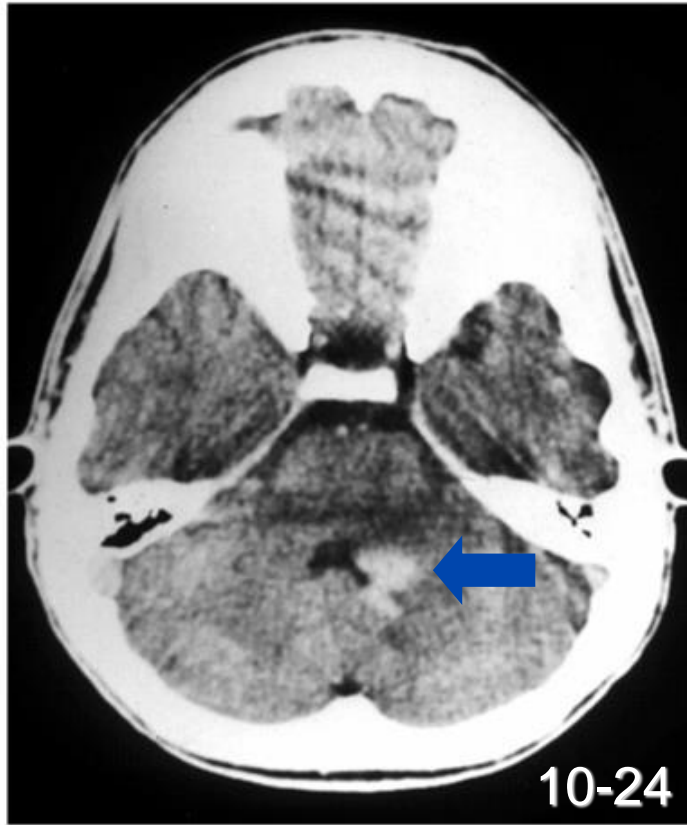


Deeper Levels

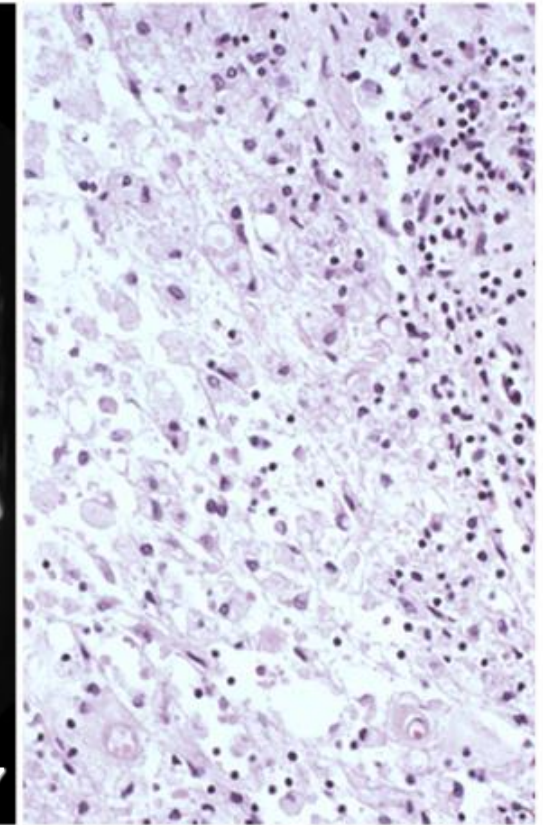
# PCNSL with steroid effect



# PCNSL with Steroid Effect

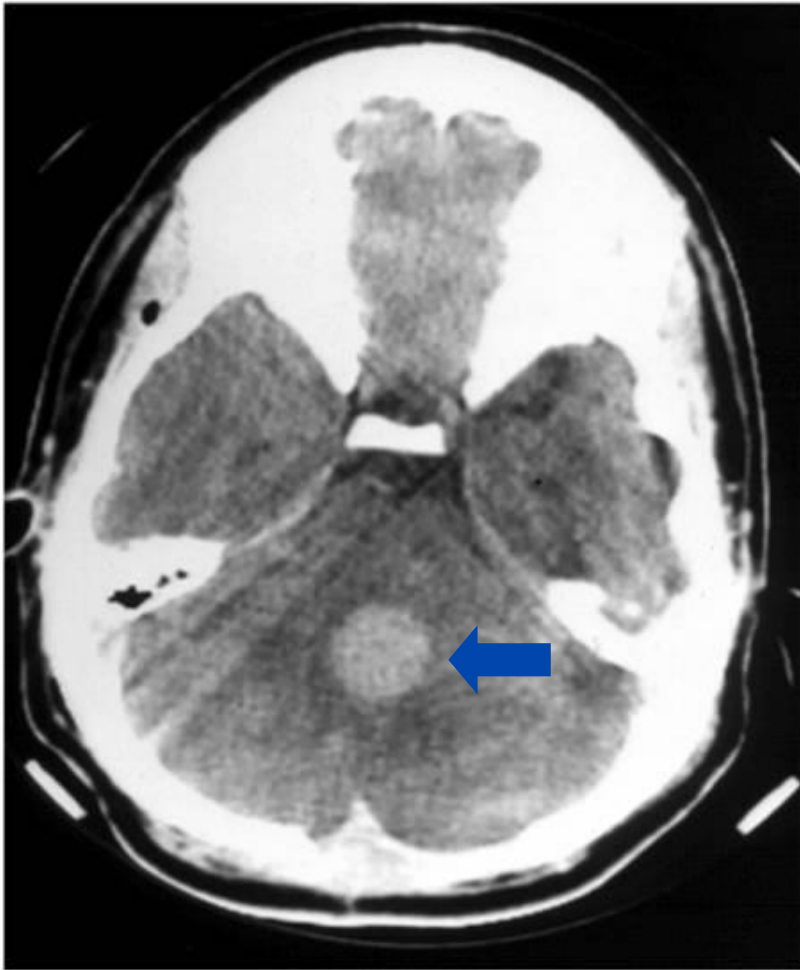


3 days steroid treatment

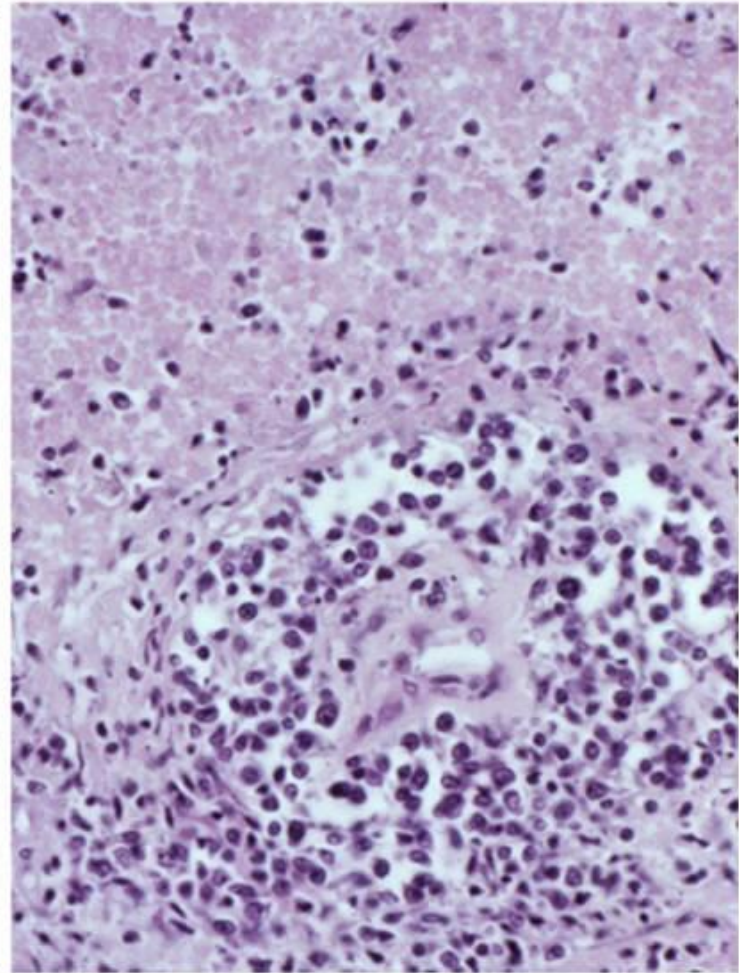


1<sup>st</sup> Biopsy

# PCNSL with Steroid Effect



Stop steroid – 1 mo later



2<sup>nd</sup> Biopsy

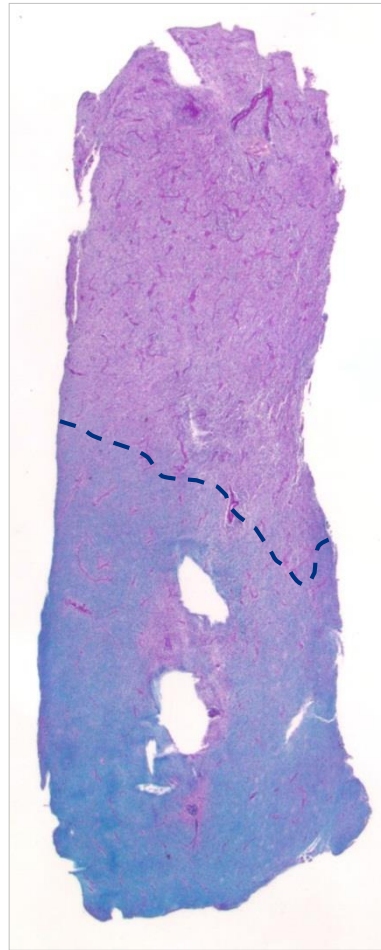
# Primary CNS Lymphoma with steroid effect

- 62-year-old man with progressive memory decline and increasing headache
- MRI: large enhancing temporal lobe mass likely GBM
- 3-week course of Decadron to reduce swelling in anticipation of surgery
- On the day of surgery, a repeat MRI demonstrated dramatic shrinking of the tumor prompting modification of the surgical plan to stereotactic biopsy

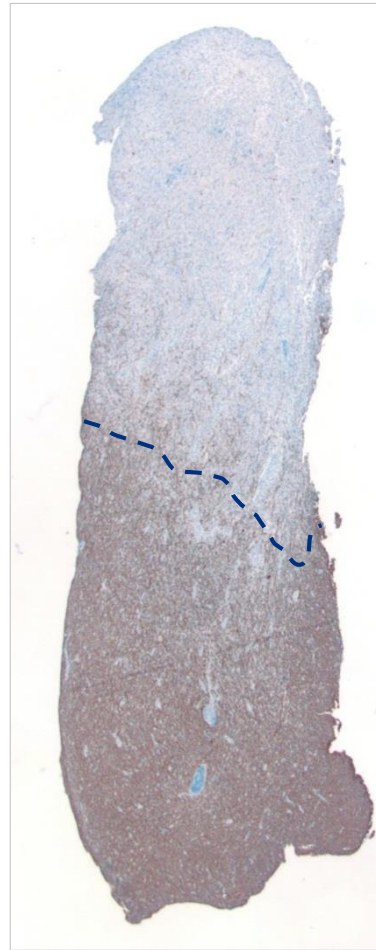
# Core Biopsy Post-Steroid



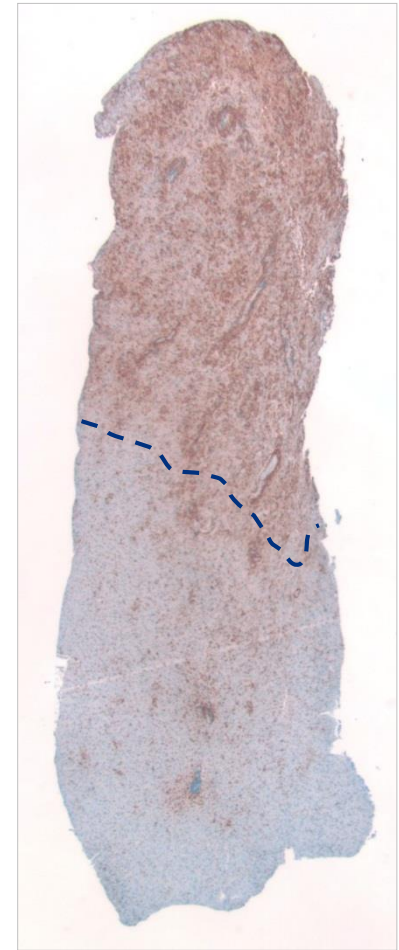
**H&E**



**LFB-PAS**



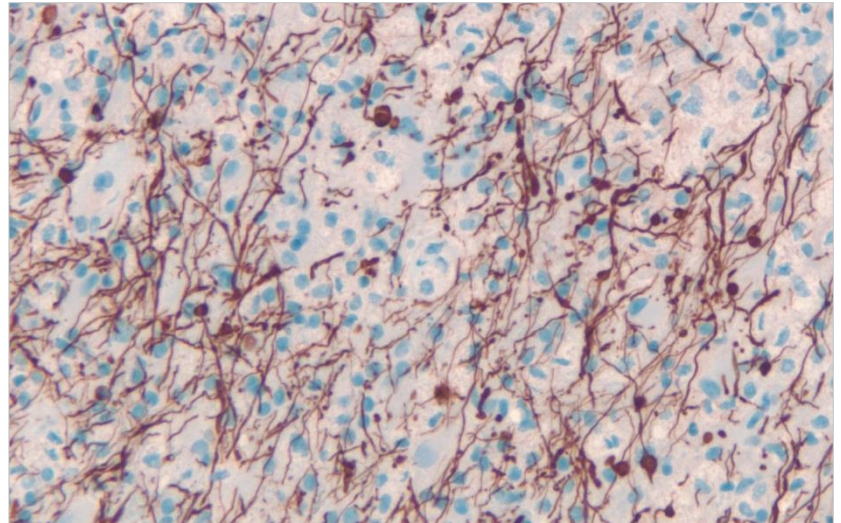
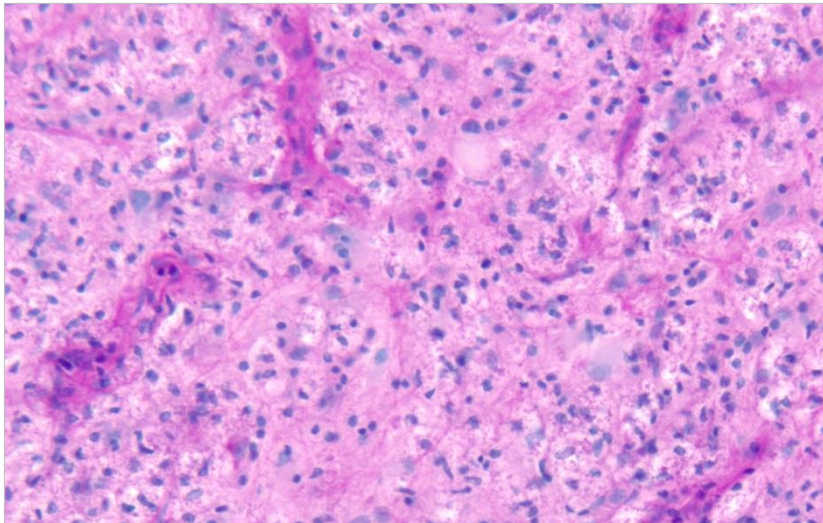
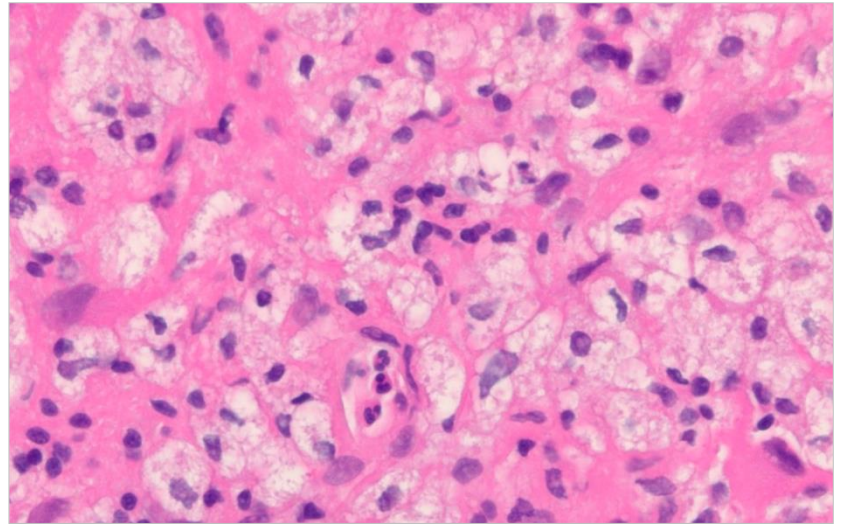
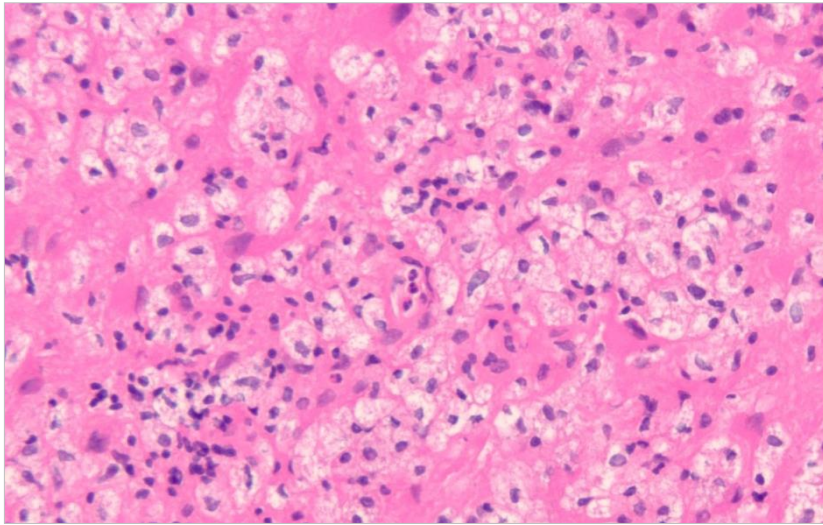
**NF**



**CD68**

*Superficially mimics demyelination*

# Core Biopsy Post-Steroid

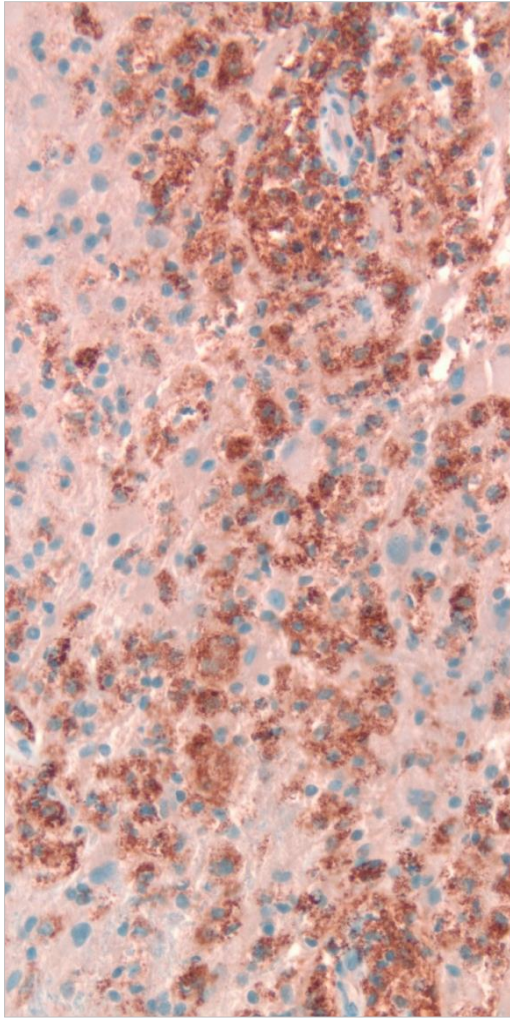


LFB-PAS

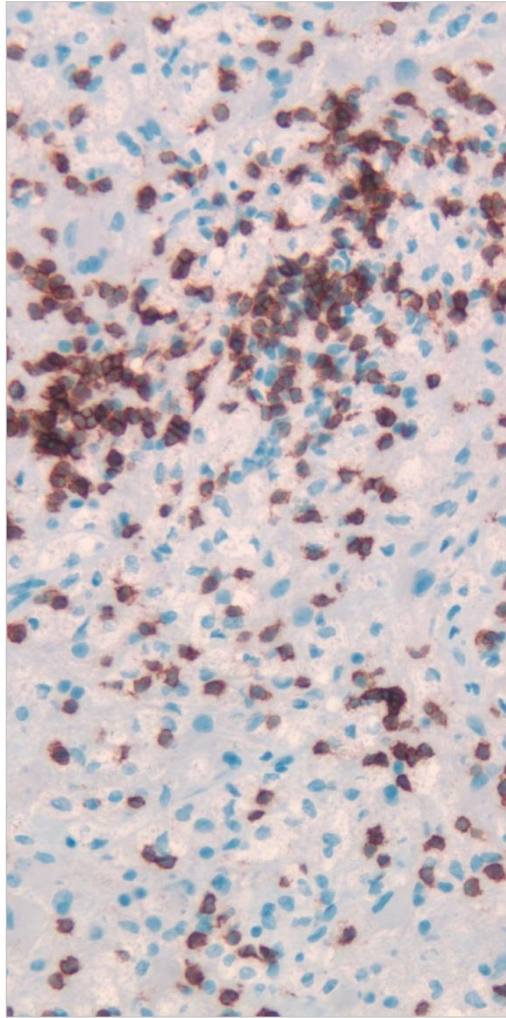
Neurofilament

*Superficially mimics demyelination*

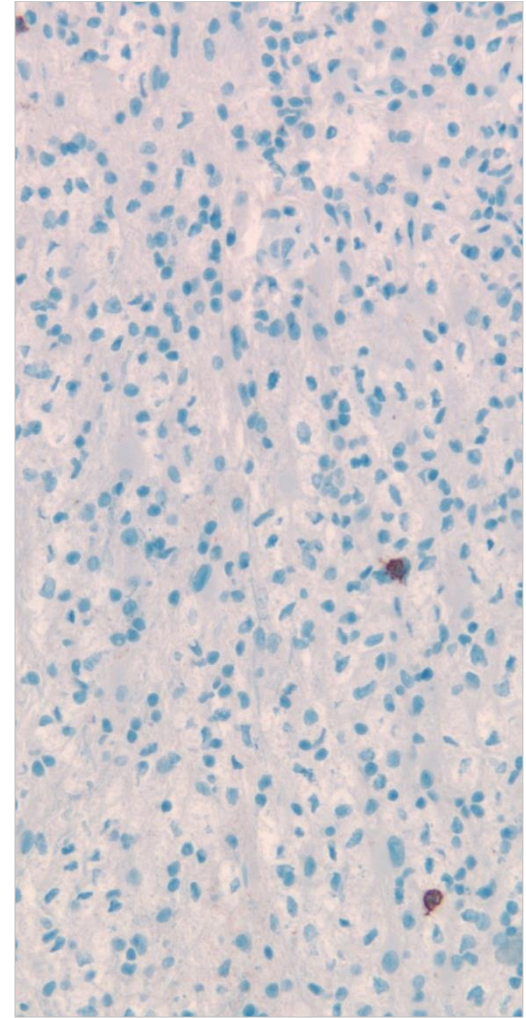
# Core Biopsy Post-Steroid



**CD68**



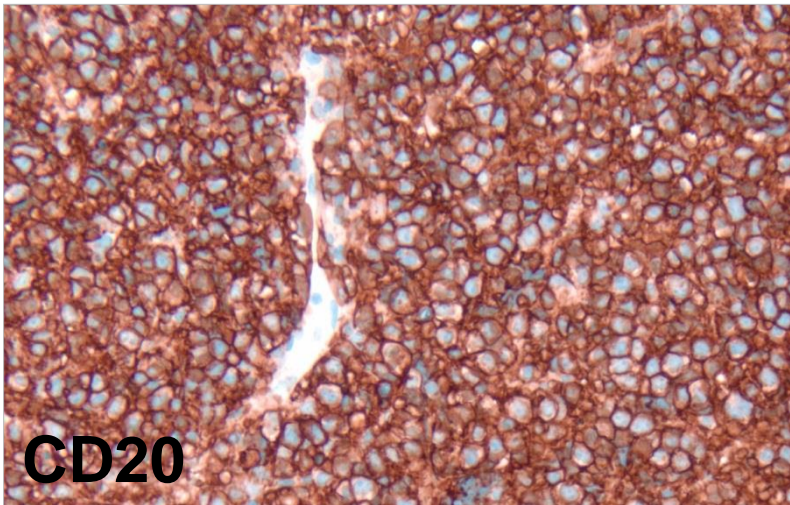
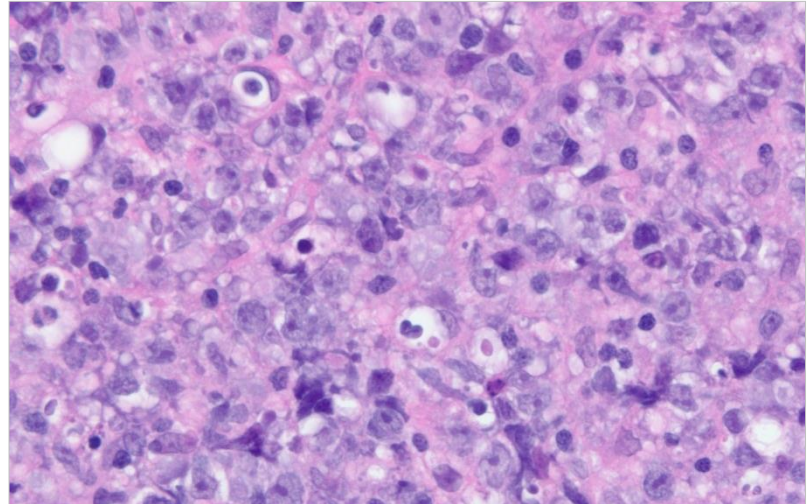
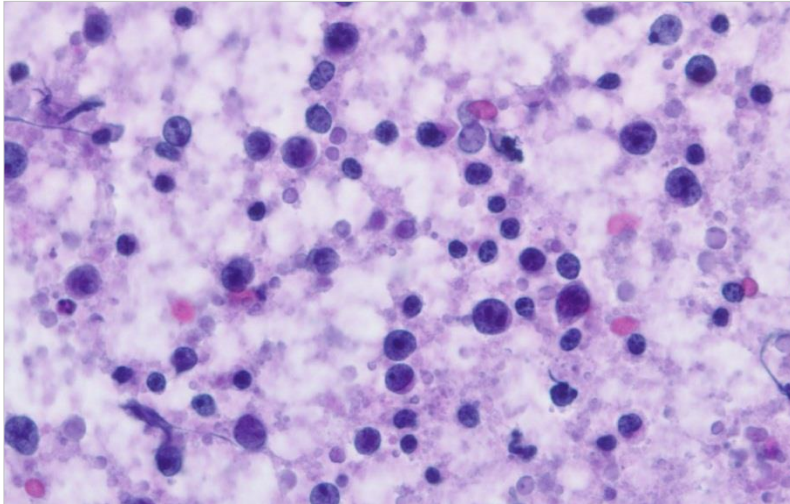
**CD3**



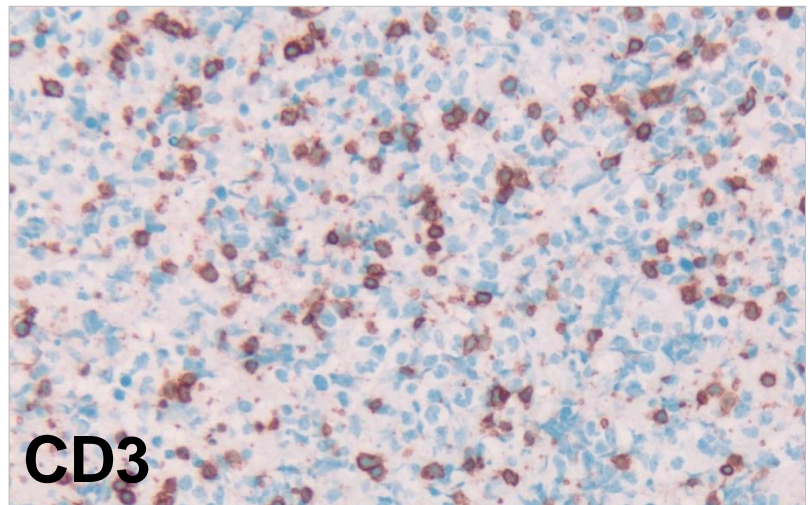
**CD20**

*Superficially mimics demyelination*

# New biopsy 3 months later



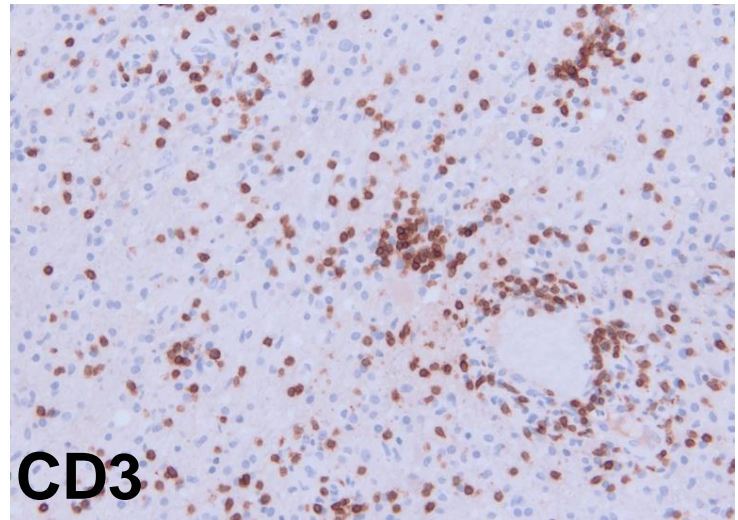
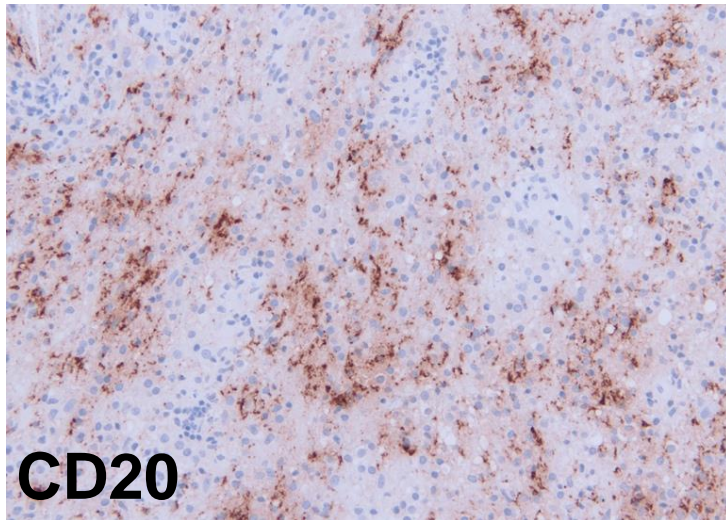
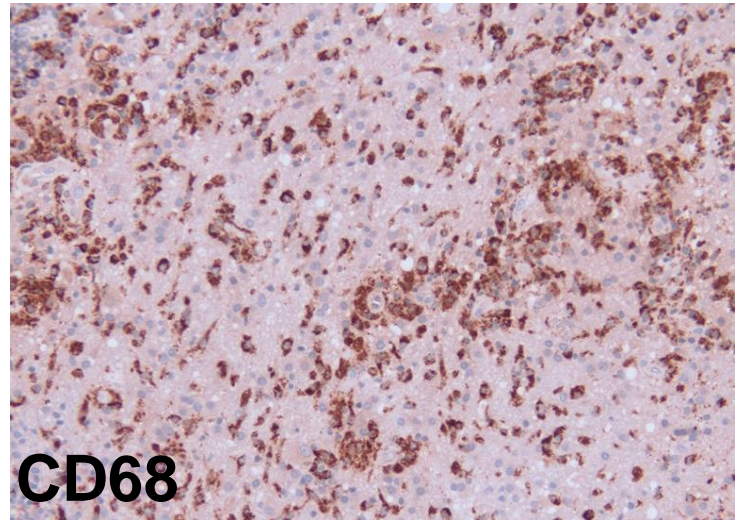
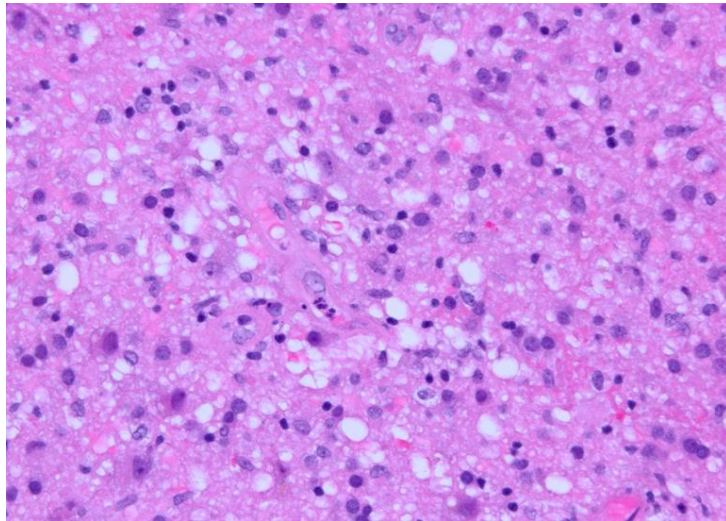
**CD20**



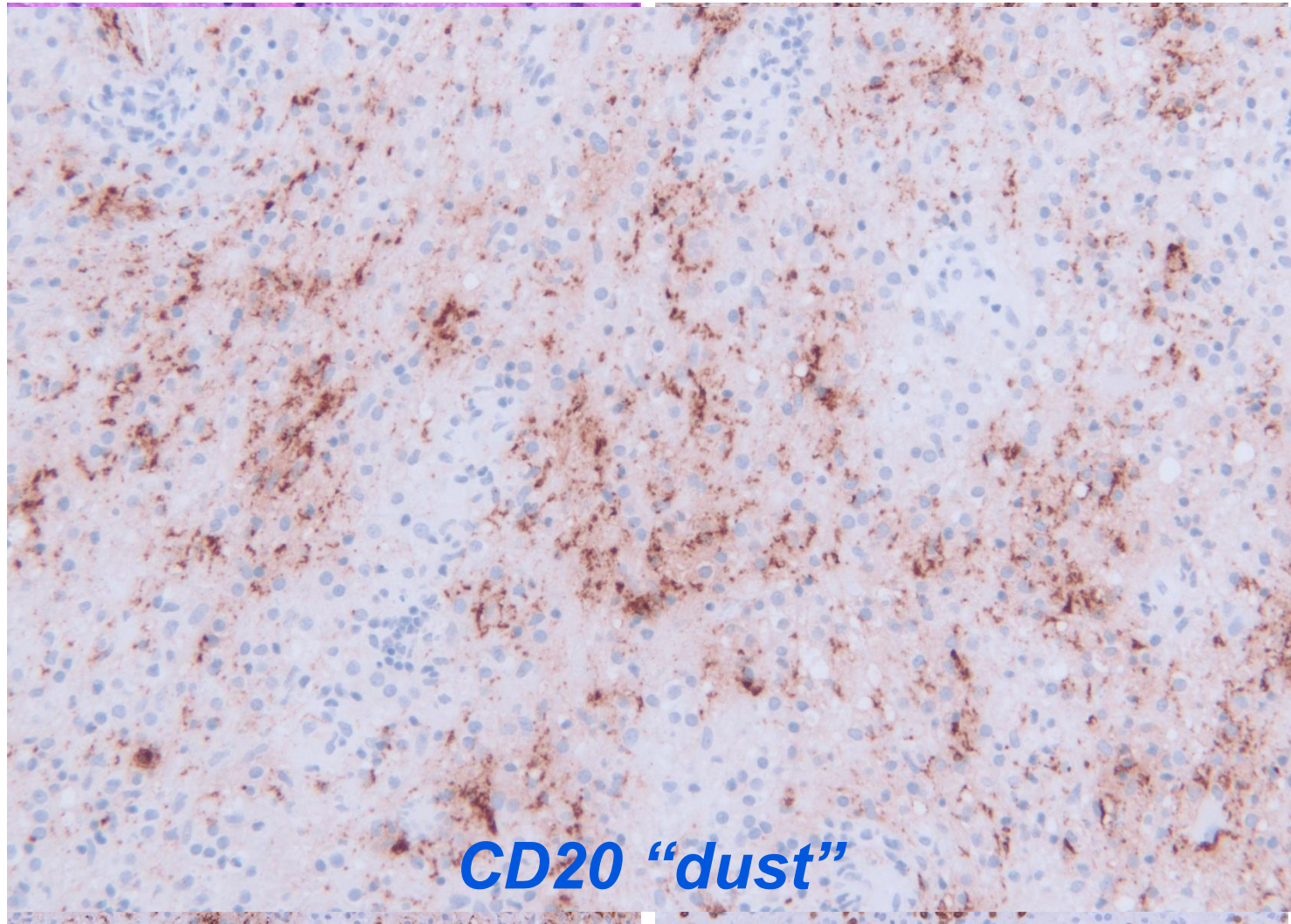
**CD3**

*Diffuse Large B-cell Lymphoma*

# PCNSL with Steroid Effect



# PCNSL with Steroid Effect



*Suspicious, but not diagnostic*

# Is a “vanishing tumor” always lymphoma?

- 12 patients with a “vanishing tumor”
  - 5 subsequently diagnosed with PCNSL
    - Age 51- 66
    - Interval to recurrence 1-24 months
    - 4 died (4-11 mo), 1 with CR alive
  - 7 patients: 2 MS, 1 infarct, 1 metastasis, 3 indeterminate
- 78 literature patients:
  - 40 (51%) PCNSL & 30 (38%) MS or ADEM
  - 2 neurosarcoid, 3 prolactinoma, 1 germinoma, 1 renal cell ca, 1 hemangioma

# PCNSL can be histologically diagnosed after corticosteroid use

*A pilot study to determine whether corticosteroids prevent the diagnosis of PCNSL*

- 13 (of 109) (12%) required a second biopsy to diagnose lymphoma
  - 8 (of 68) received steroids (12%)
  - 5 (of 39) did not (13%)
- Corticosteroids use should be determined by clinical circumstance and necessity rather than concern of obscuring PCNSL diagnosis

# Lymphoma in disguise: Sentinel Lesion

# Sentinel Lesions of Primary CNS Lymphoma

- N=4, F immunocompetent Age 49-58 (range)
- Enhancing lesions bx: non-specific inflammation, demyelination with axonal sparing (2), normal
- Three received steroids prior to biopsy
- All showed resolution of the lesions
- New symptoms and biopsy of new lesions at 7-11 mo interval disclosed large B-cell lymphoma

Alderson L et al J Neurol Neurosurg Psych 1996;60:102-105

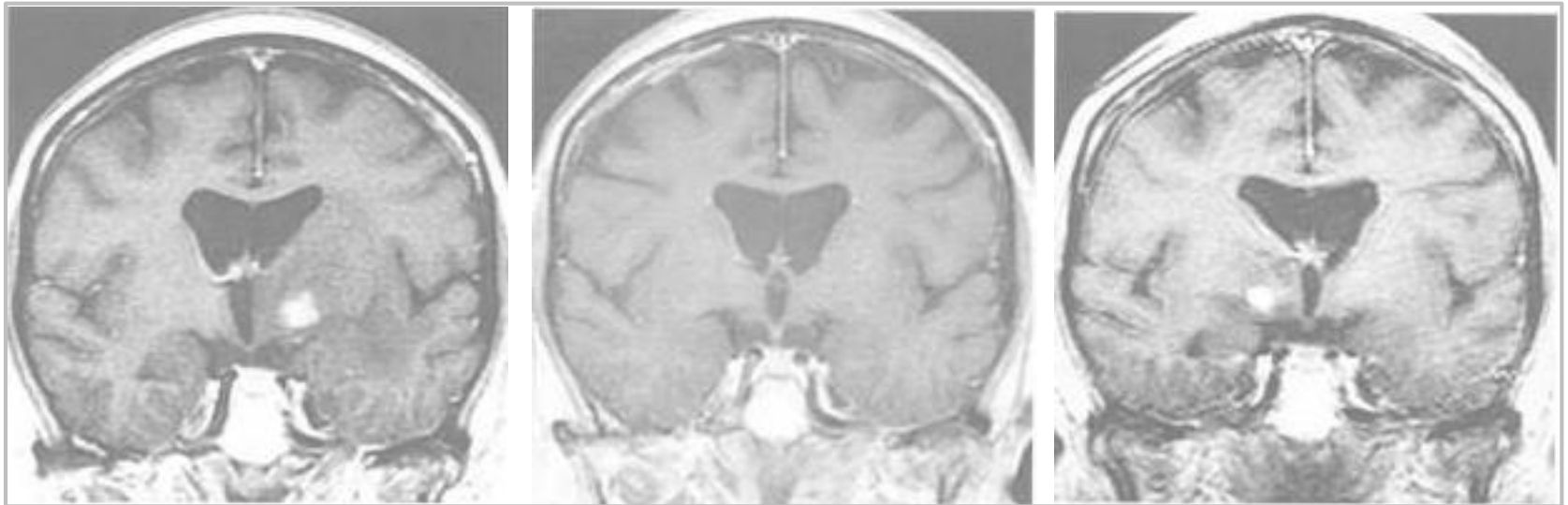
# Sentinel Lesions of Primary CNS Lymphoma

- Transient symptomatic contrast enhancing lesions, which occur in patients ultimately diagnosed with primary CNS lymphoma
- These "sentinel lesions" recede spontaneously or with corticosteroid treatment
- Diagnostic dilemma because they show variable, but non-diagnostic histopathological features.

Alderson L et al J Neurol Neurosurg Psych 1996;60:102-105

# Sentinel Lesions of Primary CNS Lymphoma

- 54-year-old F, headache, Rt arm weakness, dysarthria



April 92 —————> May 92 —————> January 93  
Biopsy (dexamethasone)

- Perivascular inflammatory cells & hypertrophic astrocytes

# Sentinel Lesions of Primary CNS Lymphoma

- “Steroid effect” may be a partial explanation
- Infiltrating T lymphocyte may plays a part in the resolution of the lesions
- Cell mediated immune response mounted against the lymphoma by immunocompetent people

Alderson L et al J Neurol Neurosurg Psych 1996;60:102-105

# Sentinel Lesions can be suspected clinically

- Patients > 50 years
- Contrast enhancing focal lesion
- Biopsy shows “demyelinating changes”
- PCNSL should be seriously considered:
  - Early discontinuation of corticosteroids
  - Repeat biopsy (in certain instances)
  - Close clinical and radiographic surveillance of the patient

Alderson L et al J Neurol Neurosurg Psych 1996;60:102-105

# Sentinel Lesions of Primary CNS Lymphoma

## Case report of unusual leukoencephalopathy preceding primary CNS lymphoma

Keith Brecher, Fred H Hochberg, David N Louis, Suzanne de la Monte, Peter Riskind

J Neurol Neurosurg Psych 1998;**65**:917–920

30 month interval

## Prolonged interval between sentinel pseudotumoral demyelination and development of primary CNS lymphoma

I Steven Ng <sup>a,\*</sup>, Helmut Butzkueven <sup>b</sup>, Renate Kalnins <sup>c</sup>, Christopher Rowe <sup>a</sup>

Journal of Clinical Neuroscience 14 (2007) 1126–1129

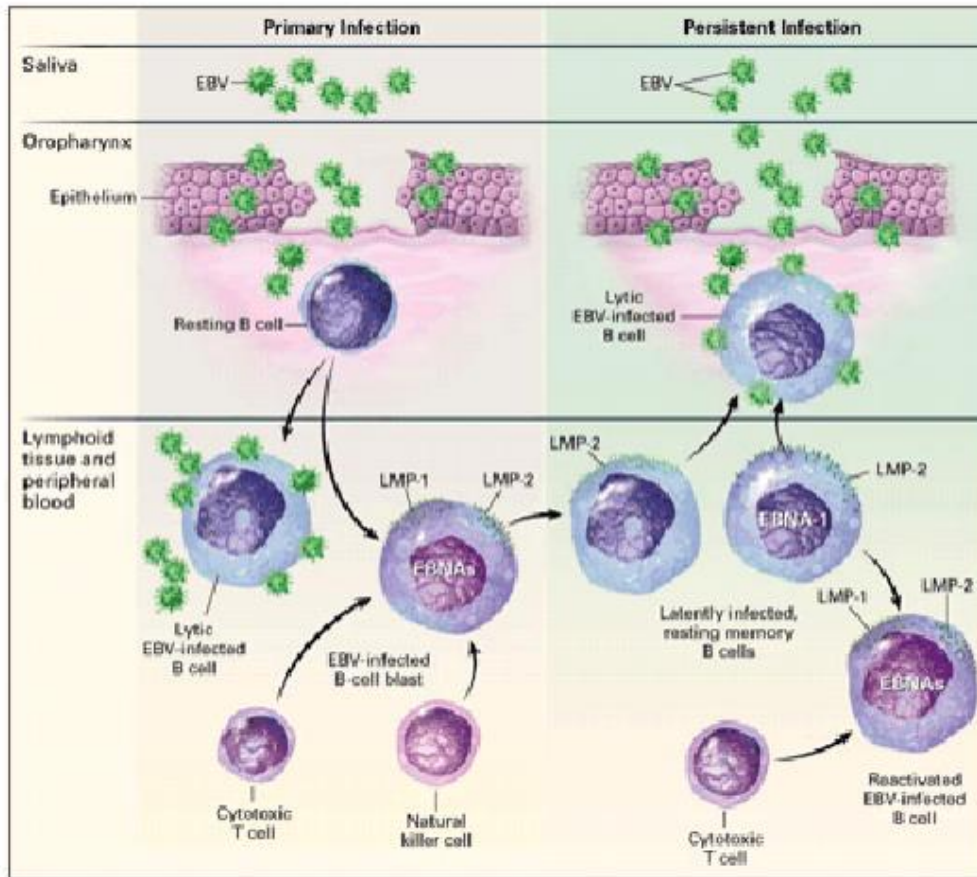
4 year interval

# Epstein-Barr Virus Associated Lymphoproliferative Disorders

# EBV Associated Lymphoproliferative Disorders

- Primary immune disorders
- Human immunodeficiency virus (HIV)
- Iatrogenic immunosuppression
  - Solid organ or bone marrow transplant (PTLD)
  - Drug related (non PTLD): methotrexate and others
- Age-related

# Epstein–Barr Virus Infection



*one of the most successful viruses, infecting over 90 % of humans and persisting for the lifetime of the person*

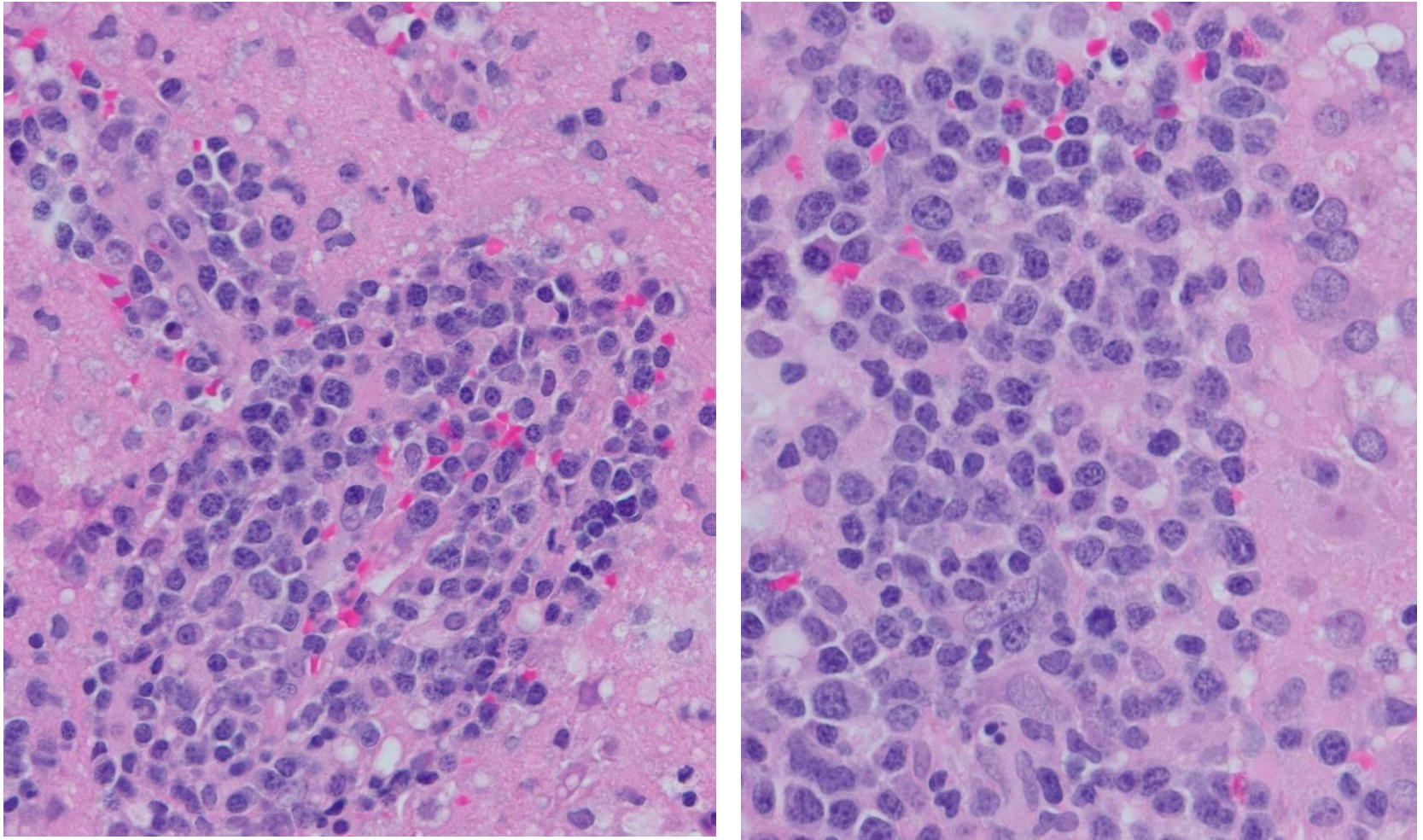
# EBV Associated Lymphoproliferative Disorders

- Polymorphous
  - Lymphoplasmacytic
- Monomorphous
  - Large B-cell lymphoma
  - Hodgkin lymphoma or HL-like lesions
  - Other lymphomas
- May regress with cessation of immunosuppression

# EBV Associated Lymphoproliferative Disorders

- Polymorphous
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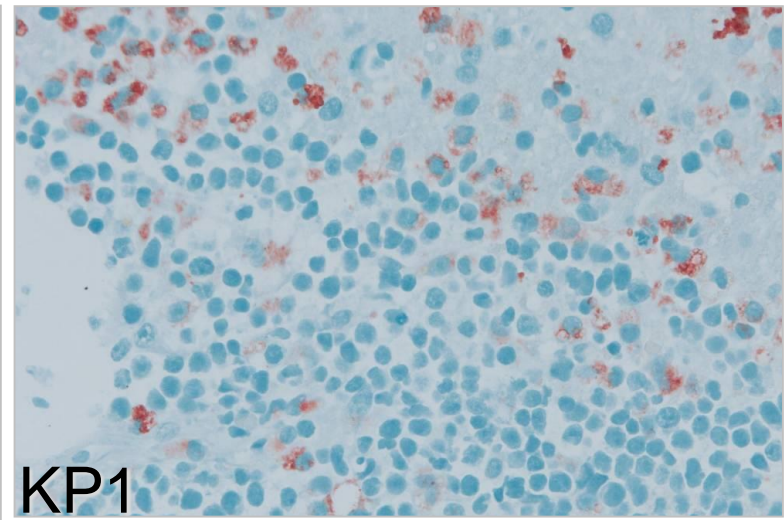
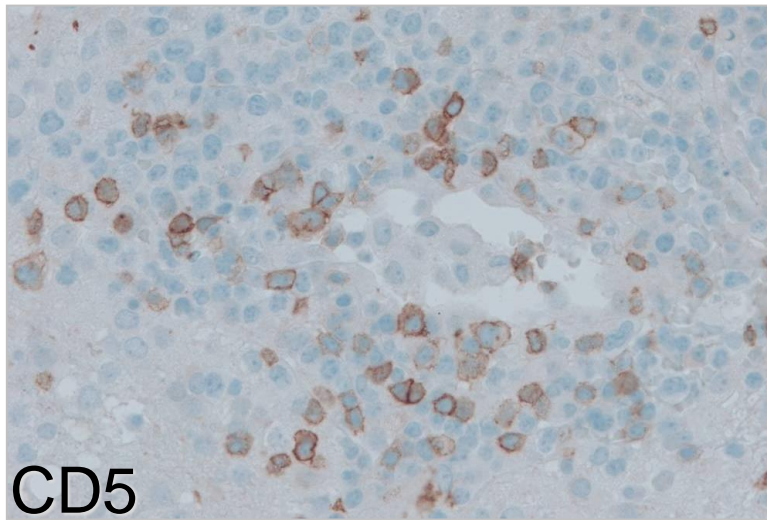
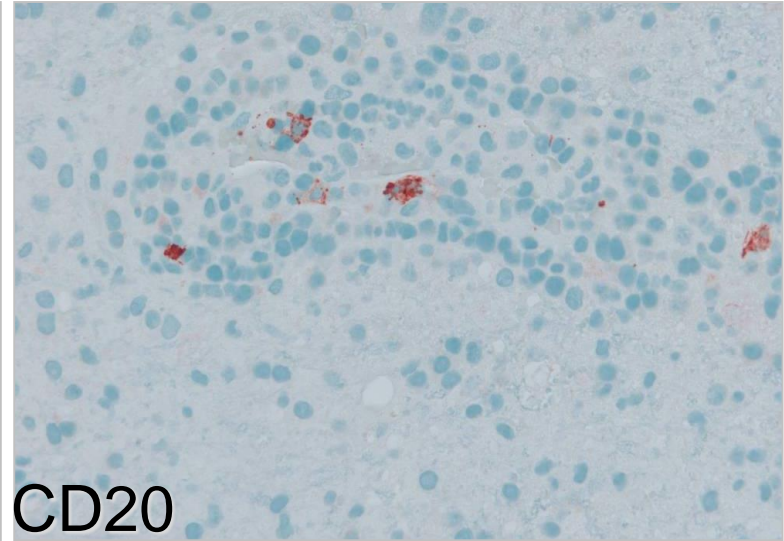
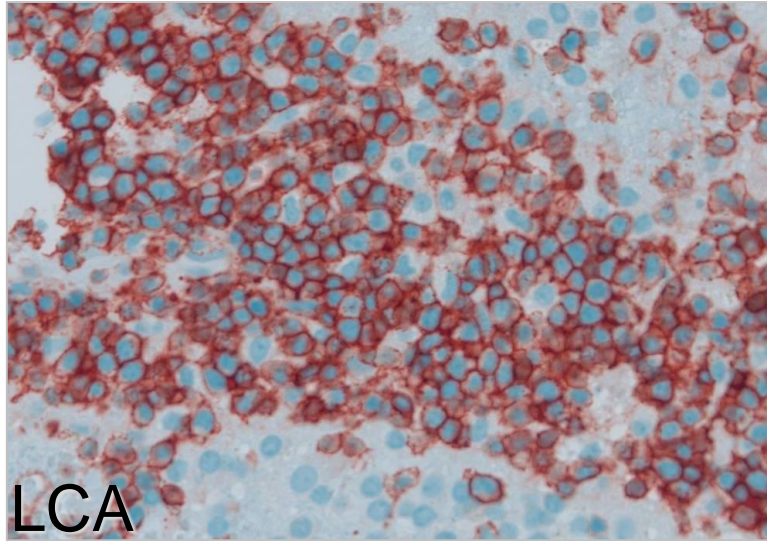
# EBV Associated Lymphoproliferative Disorders



*Polymorphous - Lymphoplasmacytic*

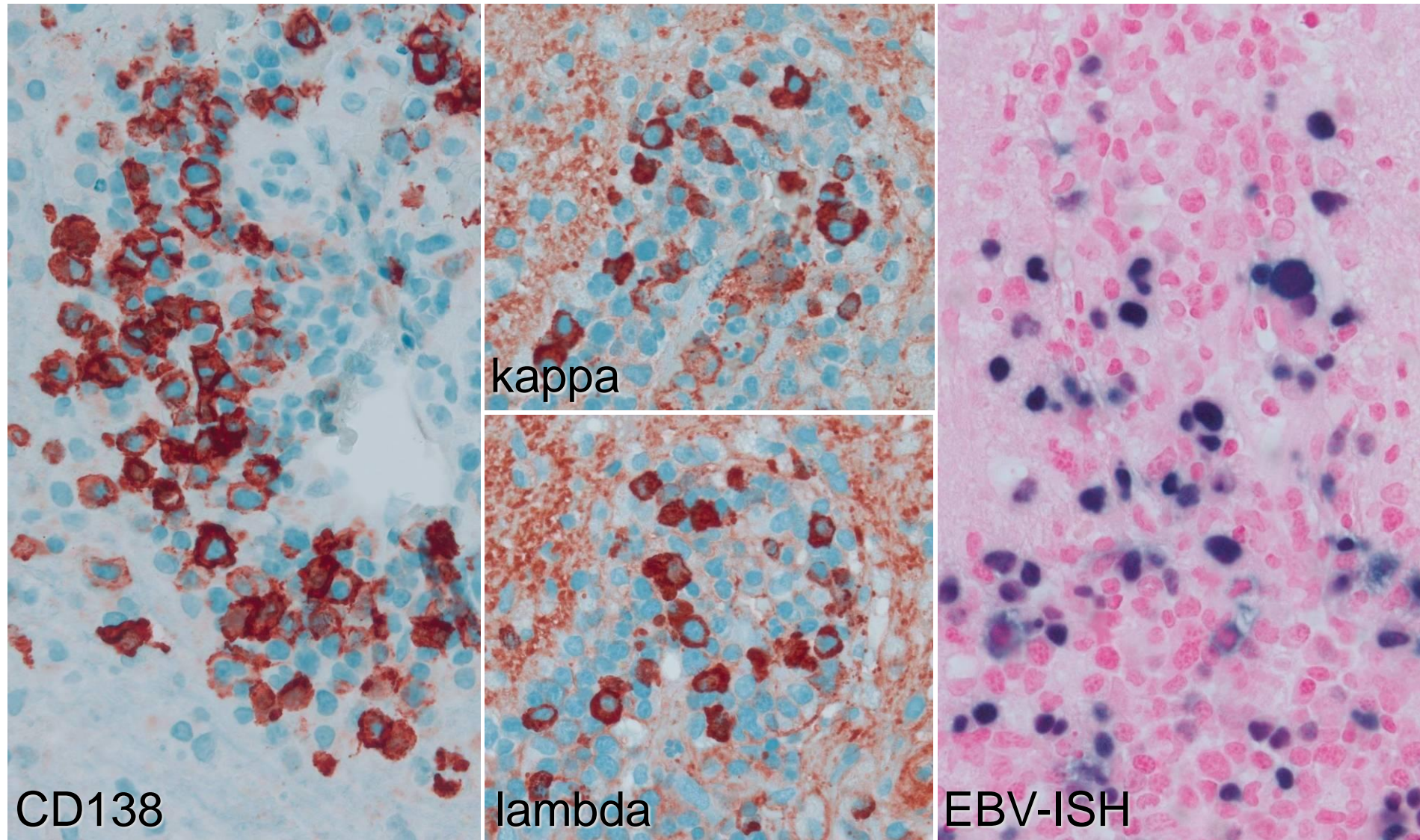
*Methotrexate Associated*

# EBV Associated Lymphoproliferative Disorders

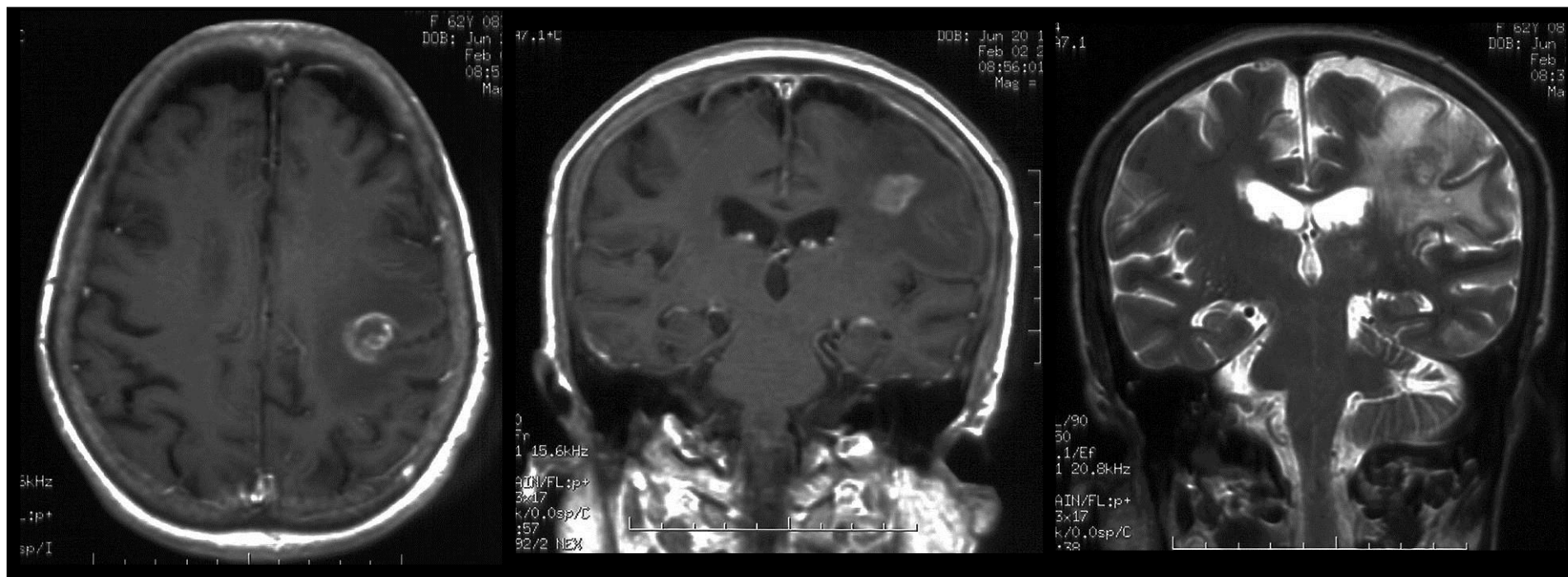


*Methotrexate Associated*

# EBV Associated Lymphoproliferative Disorders



## F 62, post kidney transplant, presents with confusion & weakness

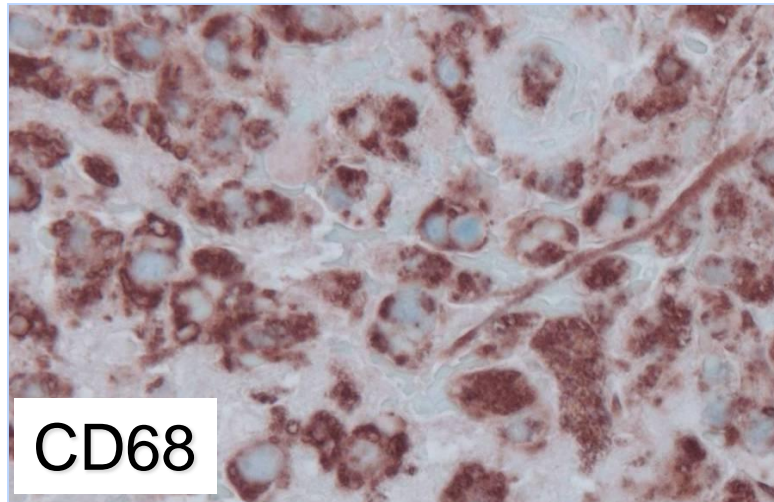
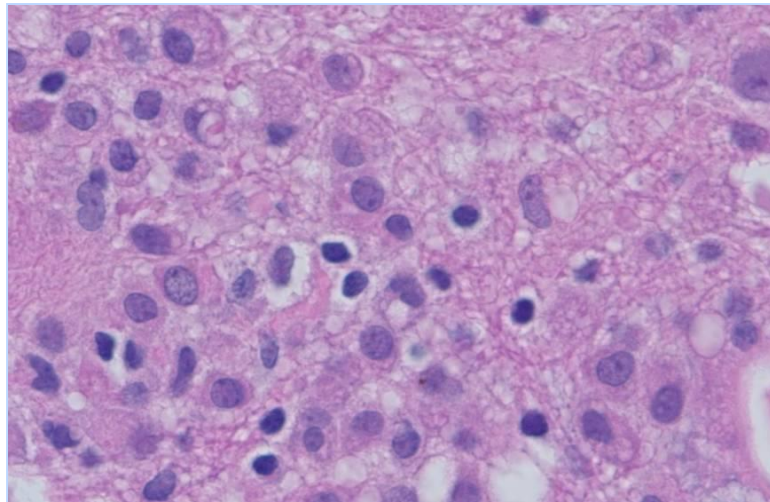
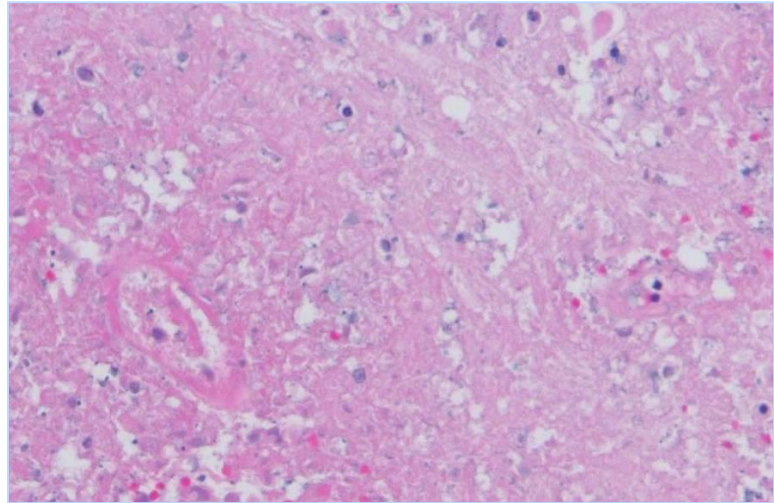
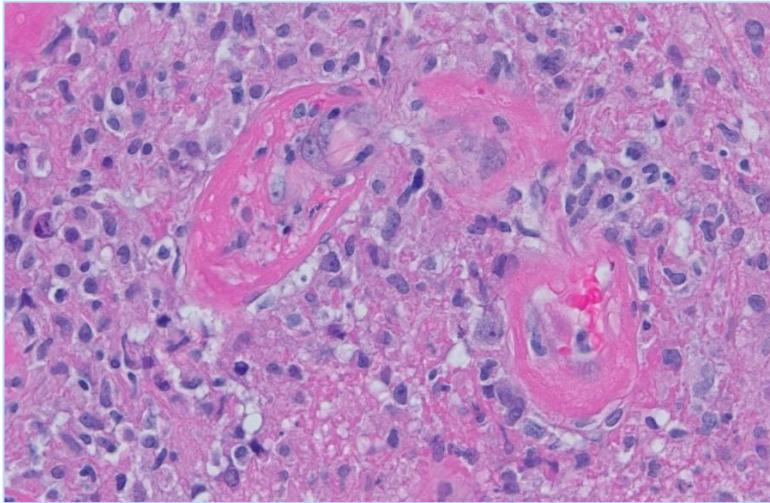


T1 with Gad

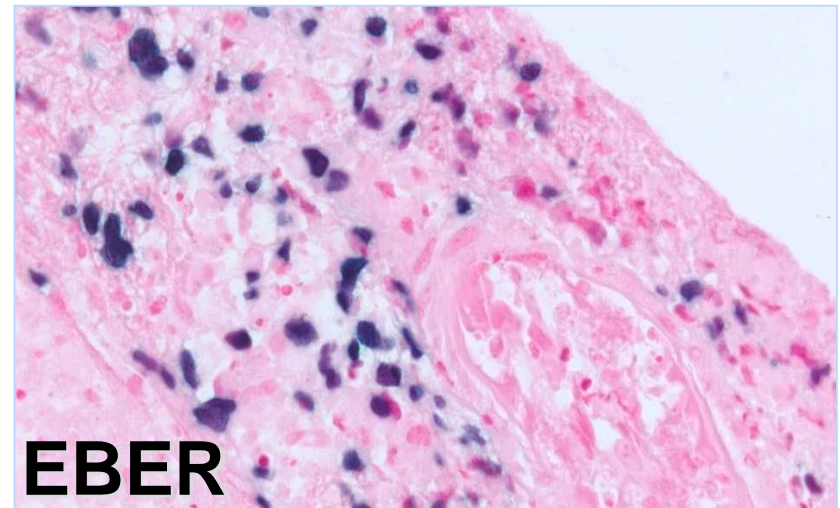
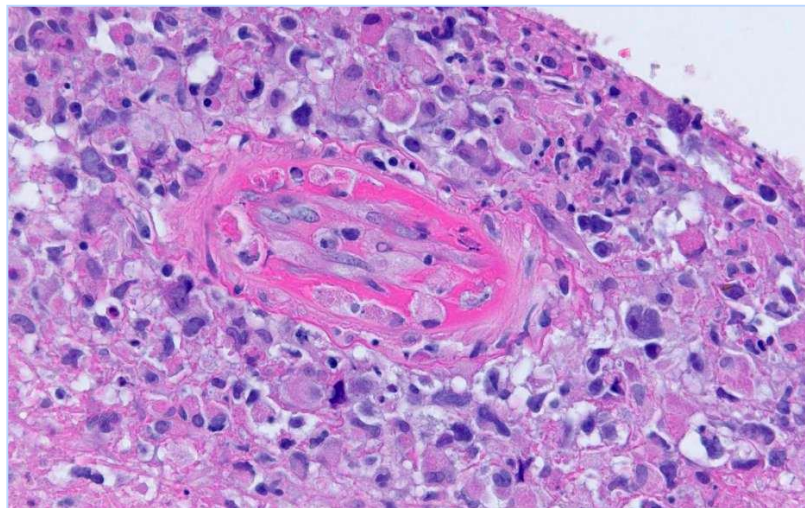
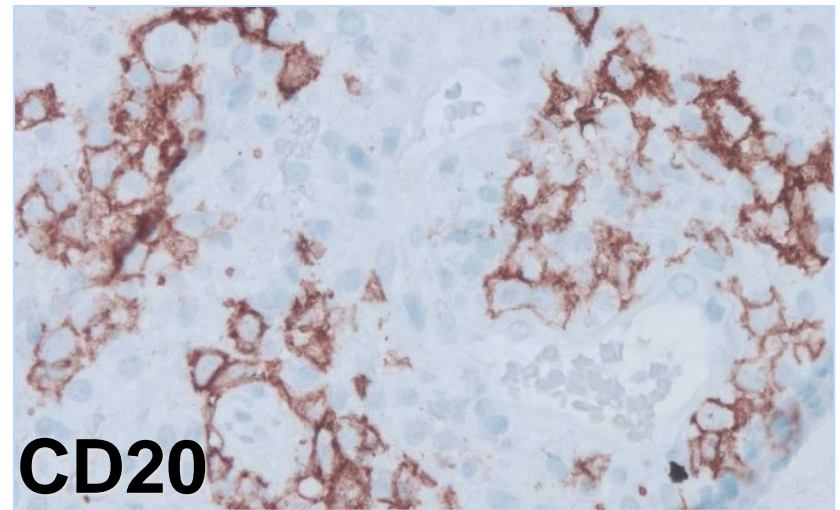
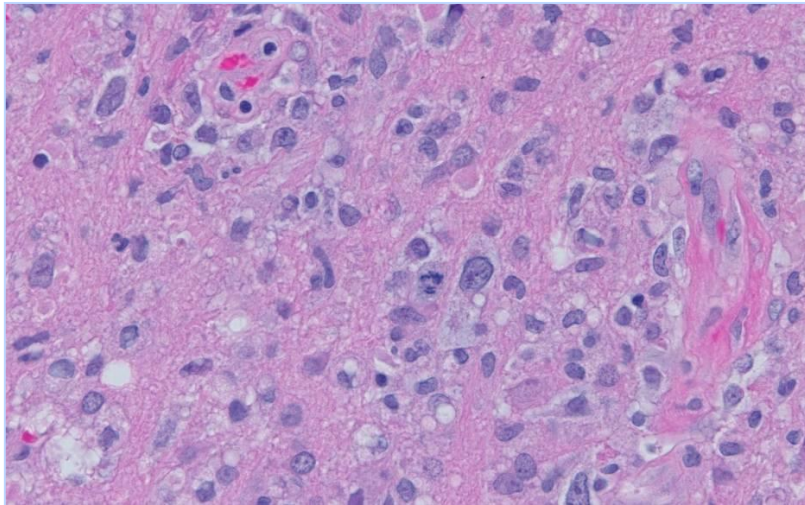
T2

*Rim enhancing mass at the gray white junction (16 mm) with surrounding edema, not present 4 months earlier*

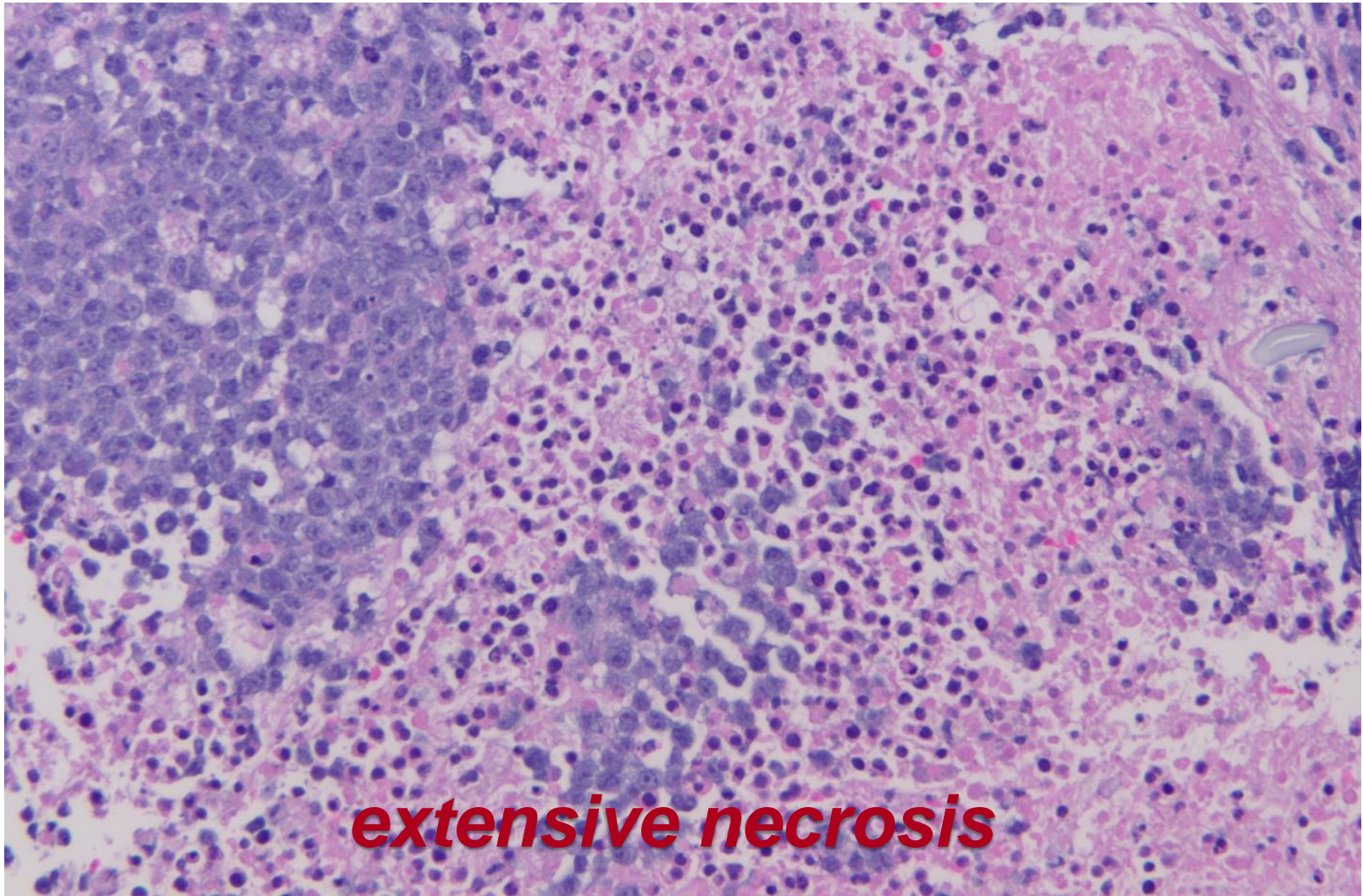
# Monomorphous PTLD (DLBCL)



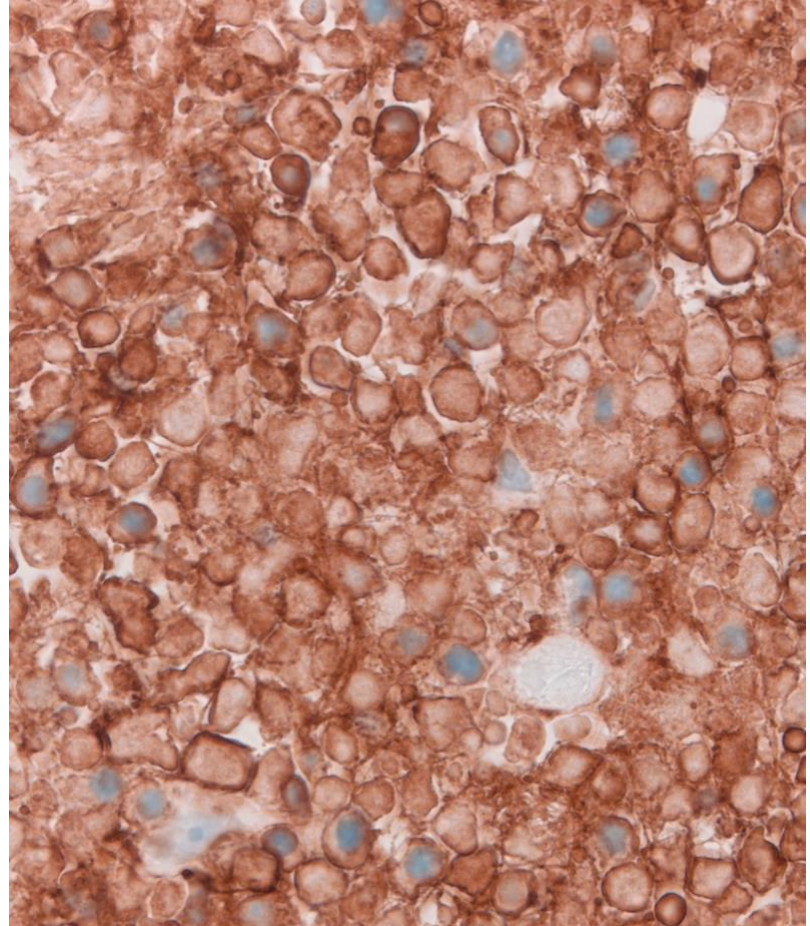
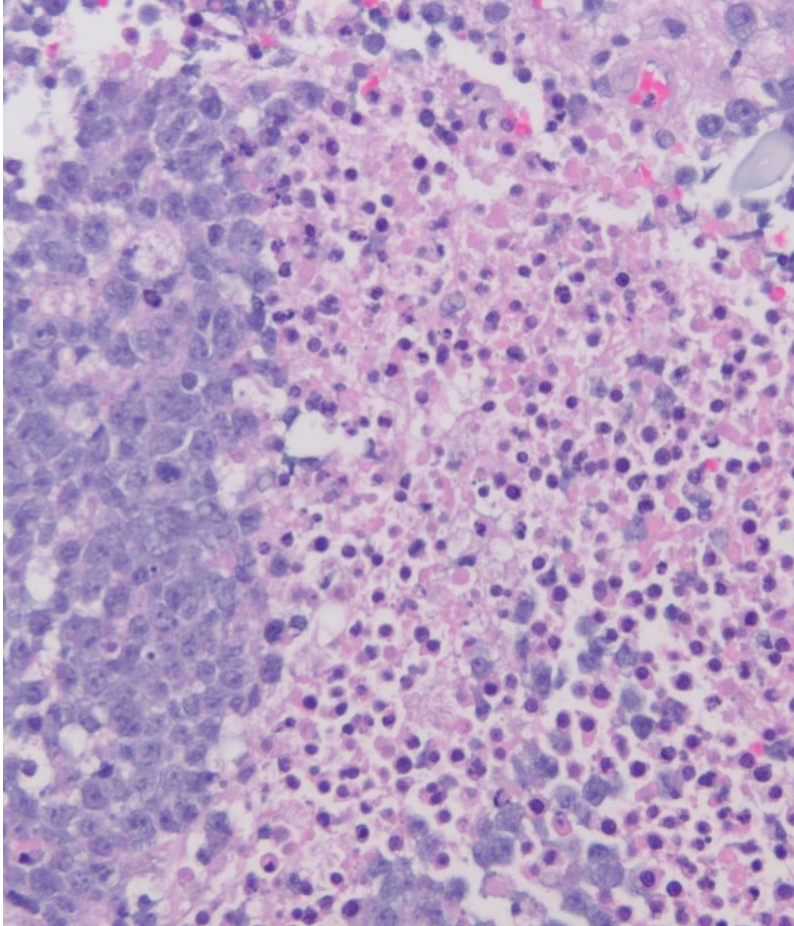
# Monomorphous PTLD (DLBCL)



# EBV Associated Lymphoproliferative Disorders

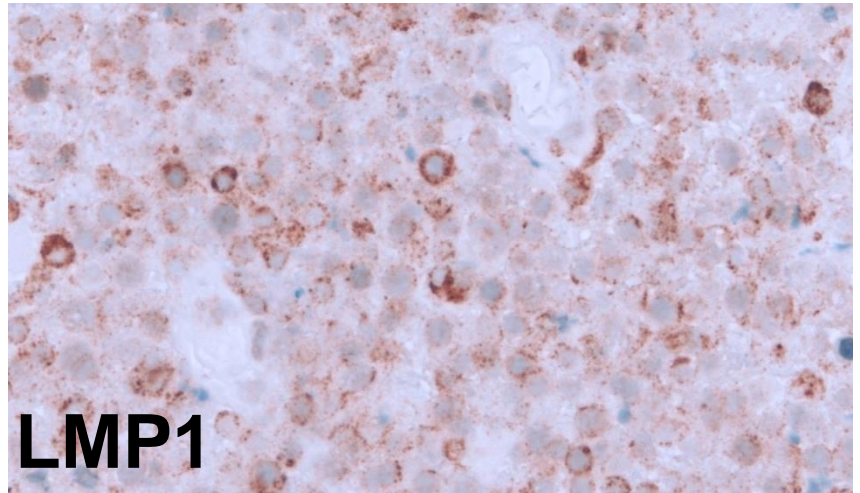
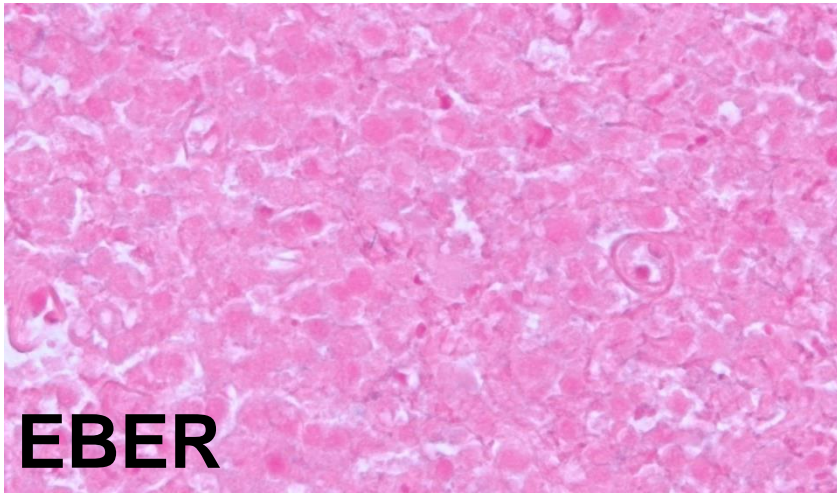
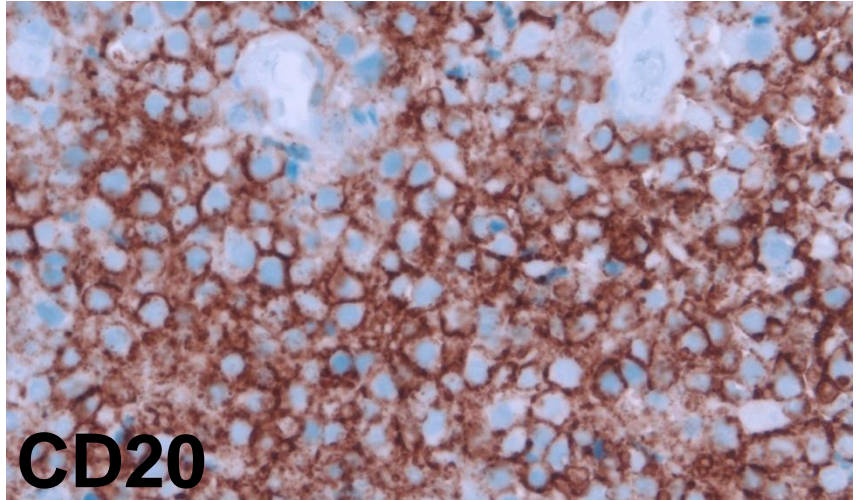
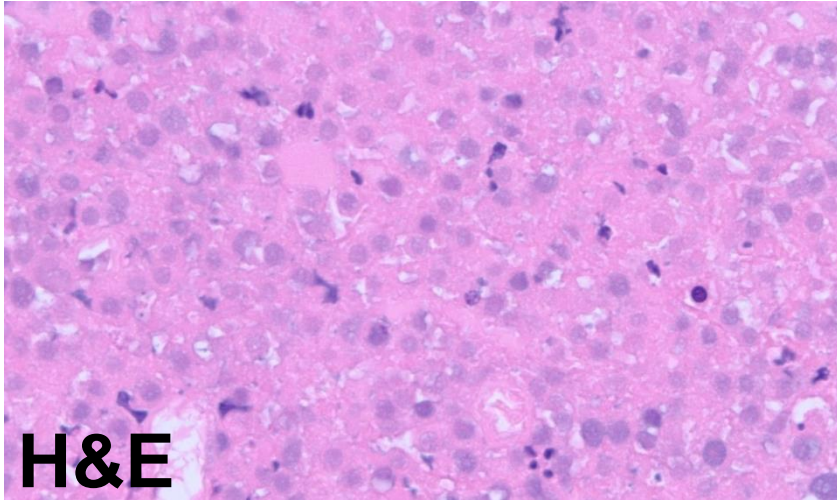


# EBV Associated Lymphoproliferative Disorders

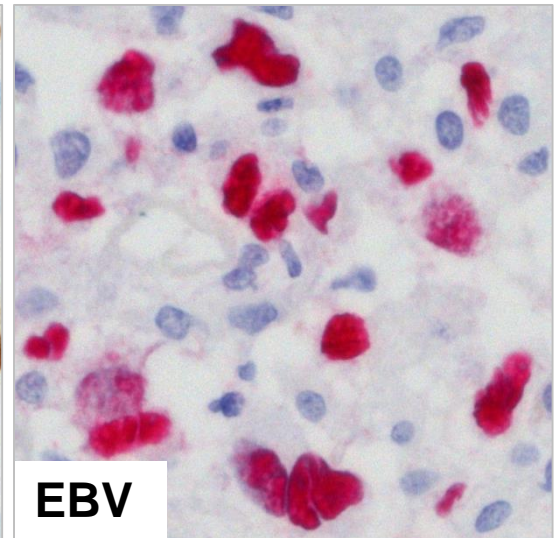
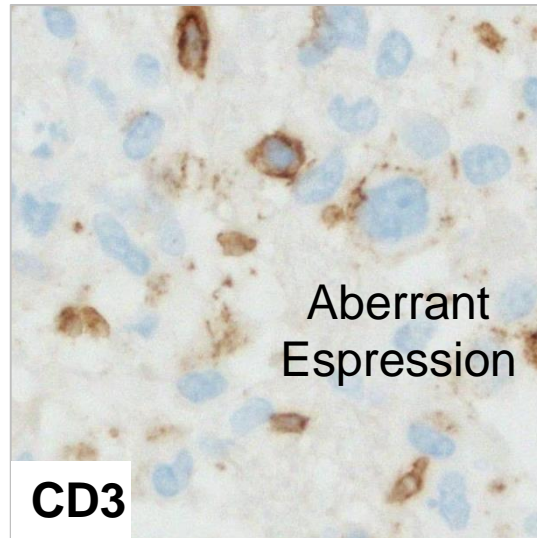
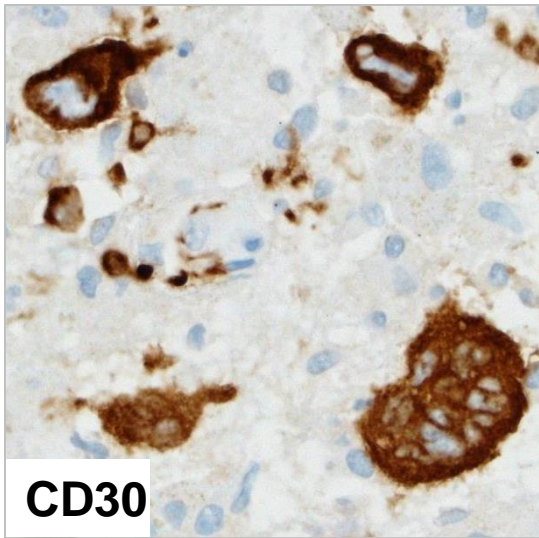
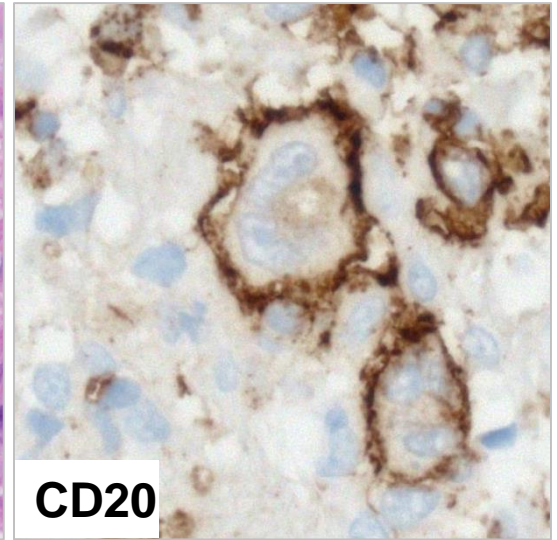
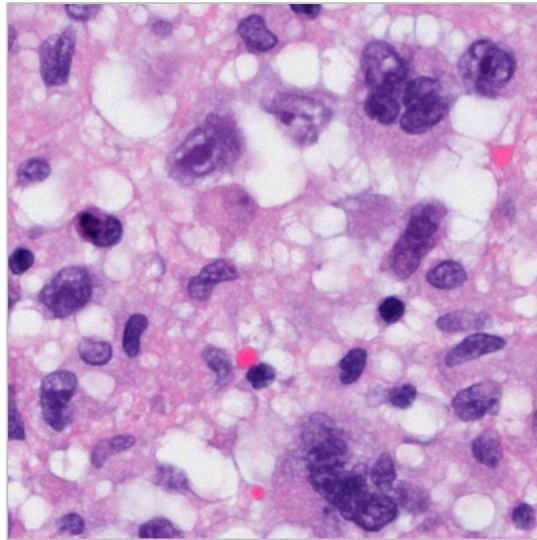
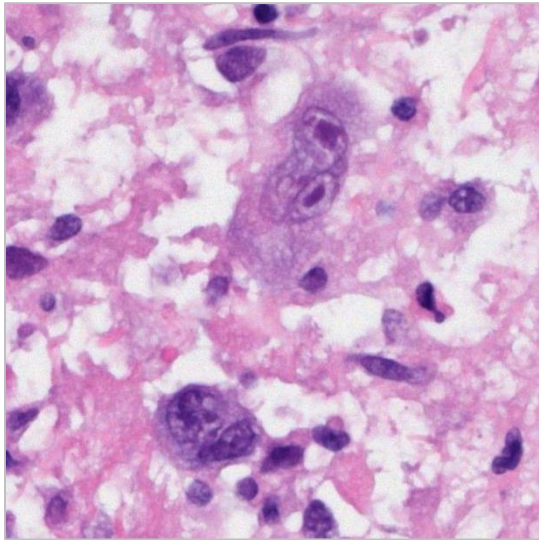


CD20 in necrotic cell “ghosts”

# EBV-associated necrotic lymphoma



# EBV Associated Lymphoproliferative Disorders



# Posttransplant primary CNS lymphoma

Thanh G. Phan, Brian P. O'Neill, and Paul J. Kurtin

*Department of Neurology (T.G.P., B.P.O.) and the Division of Hematopathology (P.J.K.), Mayo Clinic and Mayo Foundation, Rochester, MN 55905*

- N= 8      4F, 4M      age 34-50 yrs
- Kidney (4), plus pancreas (2), liver (1), lung (1)
- Focal neurology exam (6)
- Abnormal imaging
- Biopsy: stereotactic (6), open (2)
- Hemorrhage post biopsy (4), 2 deaths
- Six patients died (median survival 13 wks)

Neuro-Oncology 2007;9:364-9

## **EBV-associated lymphoproliferative disorder of CNS associated with the use of mycophenolate mofetil**

Brian Patrick O'Neill, Steven Vernino, Ahmet Dogan, and Caterina Giannini

*Departments of Neurology (B.P.O.) and Laboratory Medicine (A.D., C.G.), Mayo Clinic and Foundation and the Mayo Clinic Cancer Center, Rochester, MN 55905; and Department of Neurology (S.V.), University of Texas Southwestern Medical Center, Dallas, TX 75390; USA*

J Neuropathol Exp Neurol  
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Vol. 67, No. 11  
November 2008  
pp. 1103–1111

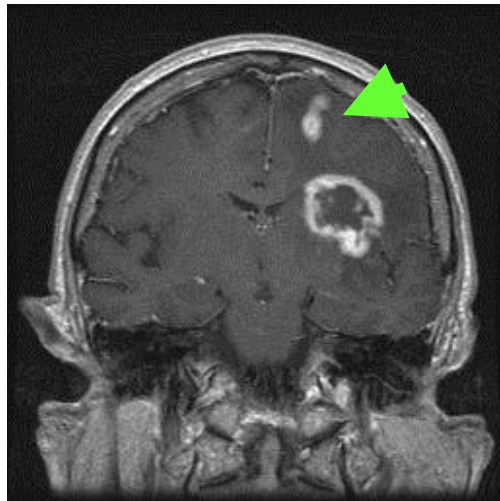
### ORIGINAL ARTICLE

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## **Epstein Barr Virus-Associated Primary CNS Lymphomas in Elderly Patients on Immunosuppressive Medications**

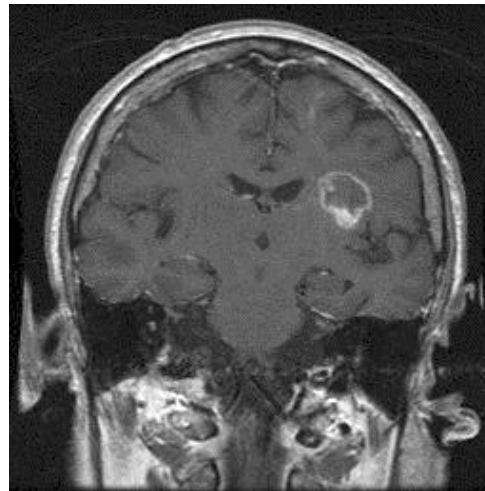
B.K. Kleinschmidt-DeMasters, MD, Denise M. Damek, MD, Kevin O. Lillehei, MD, Ahmed Dogan, MD, PhD, and Caterina Giannini, MD, PhD

# Primary CNS lymphoma complicating treatment of myasthenia gravis with mycophenolate mofetil



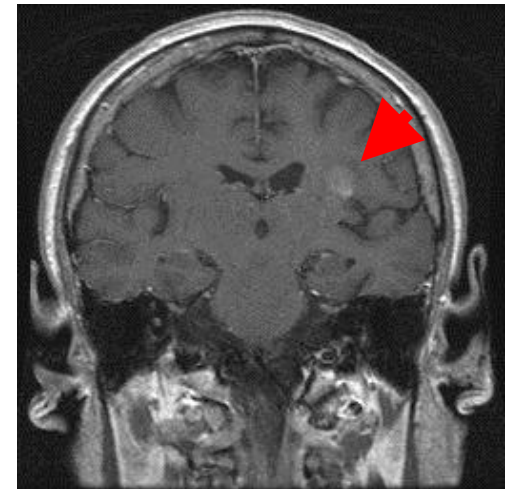
July 03

Biopsy

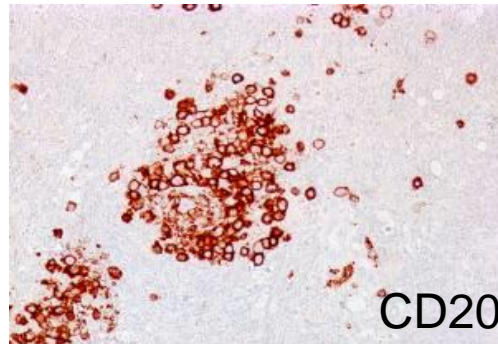
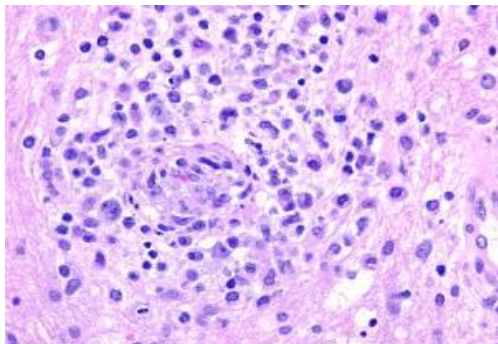


Sept 03

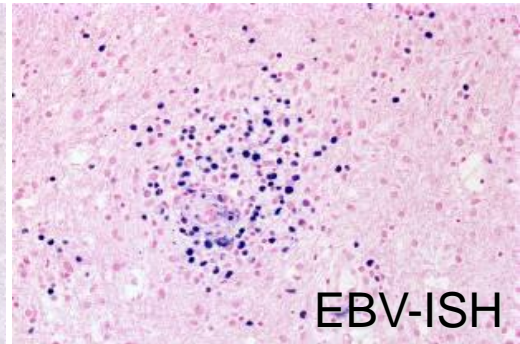
MM withdrawal



June 04



CD20



EBV-ISH

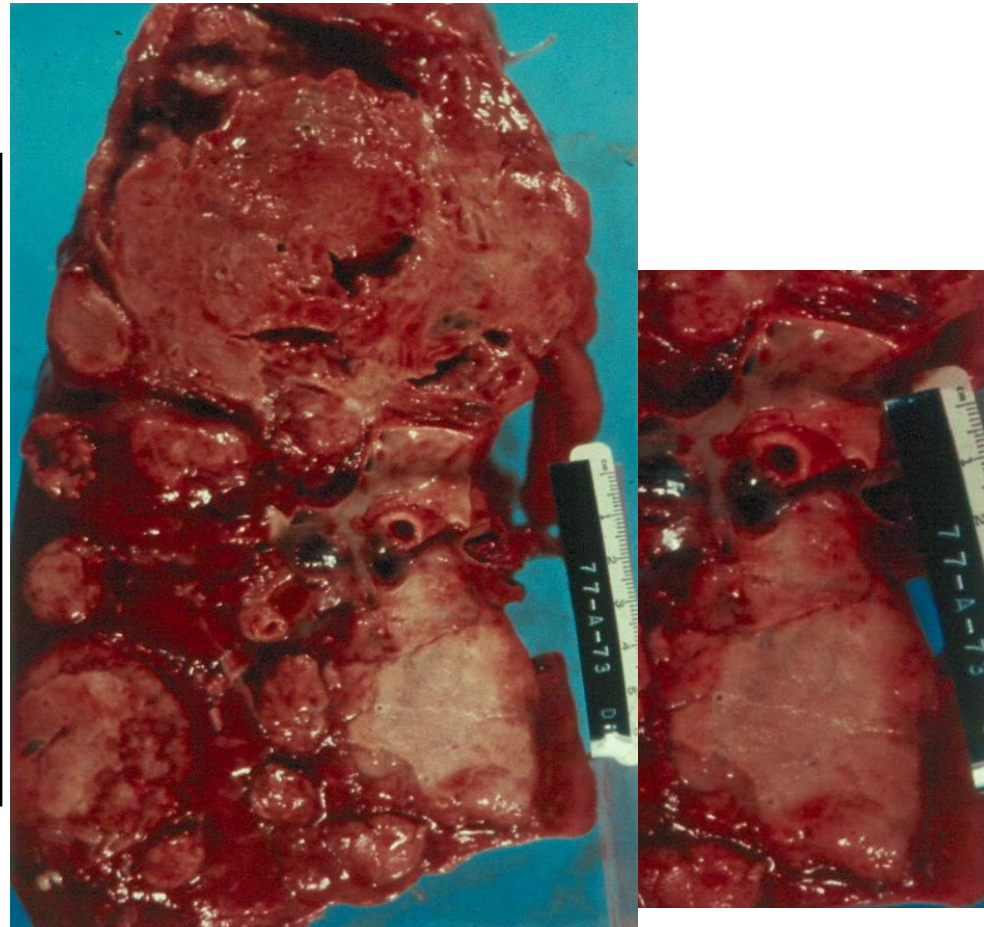
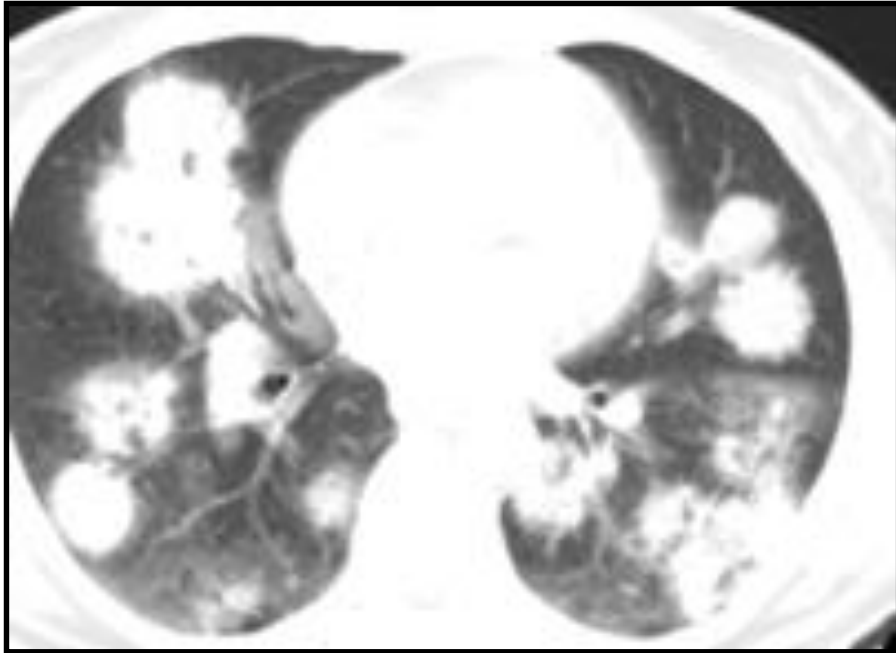
# Lymphomatoid Granulomatosis

## What is it? Where does it fit?

# Lymphomatoid Granulomatosis

- Distinct clinicopathologic entity - Liebow & al 1972
- Characteristic histologic triad:
  - (1) polymorphic lymphoid infiltrate (large atypical cells)
  - (2) angiitis,
  - (3) "granulomatosis"
- Clinically, M>F, typically 5<sup>th</sup> – 6<sup>th</sup> decade
- Respiratory symptoms (cough, dyspnea), fever, malaise, weight loss
- Skin (37%) & CNS (30%) involvement

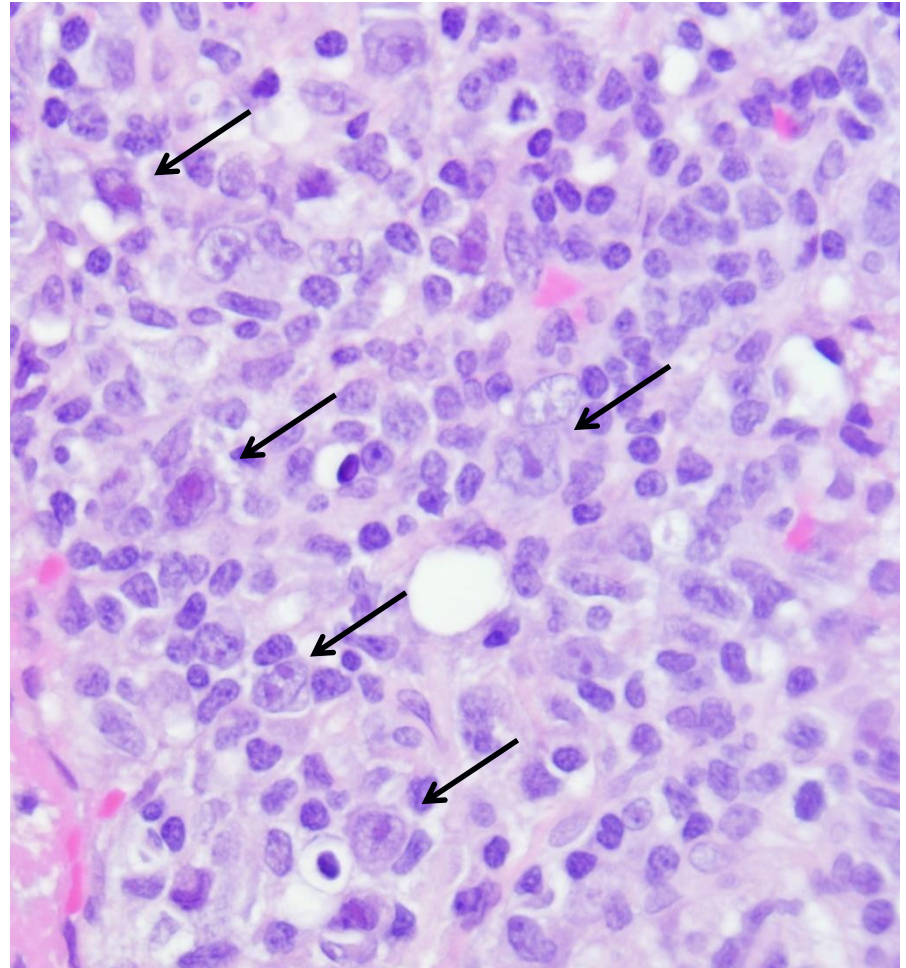
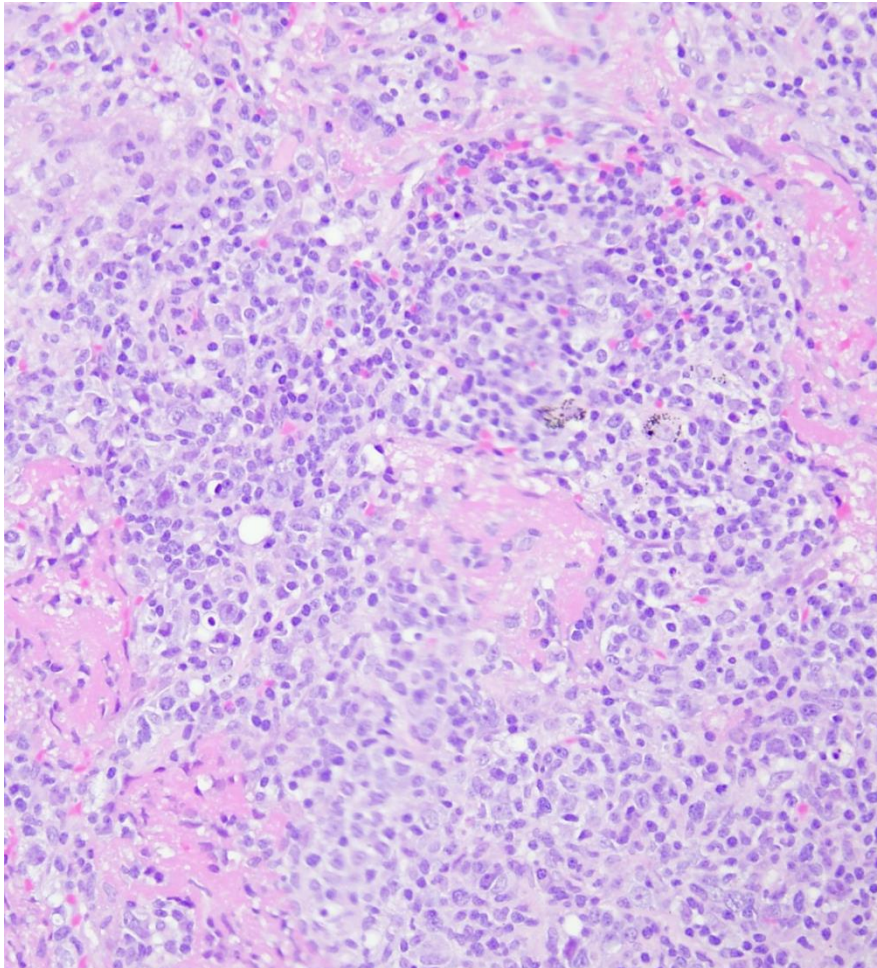
# Lymphomatoid Granulomatosis



Lee et al. AJR 2000;175:1335

From Dr Liebow's original cases (courtesy of Dr Yi)

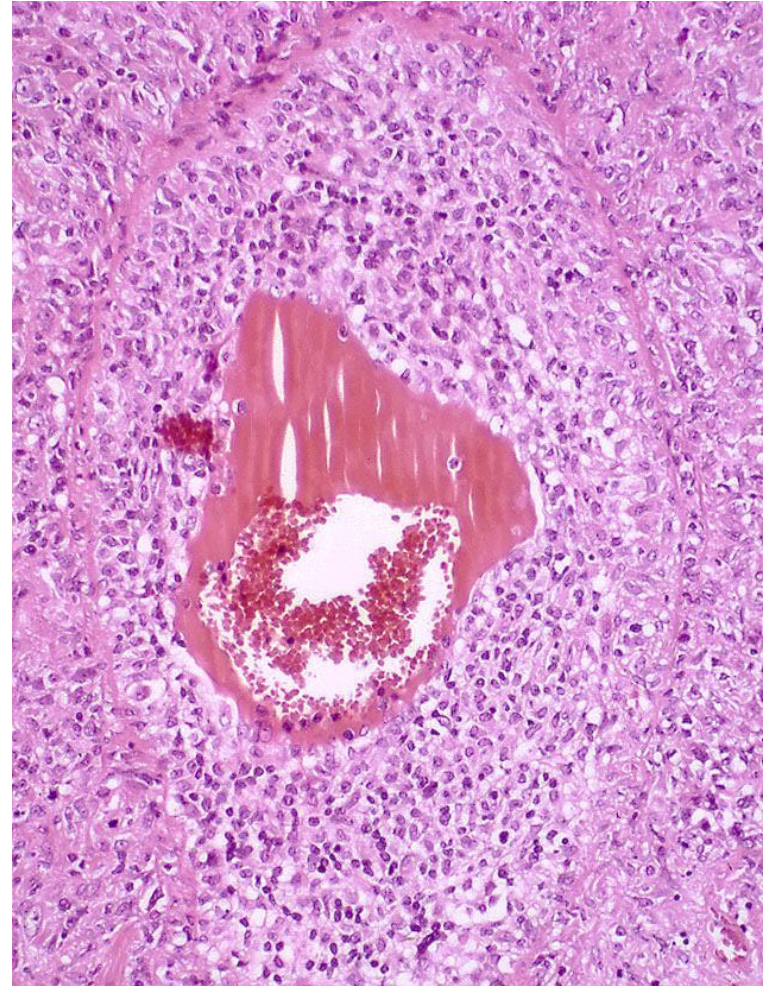
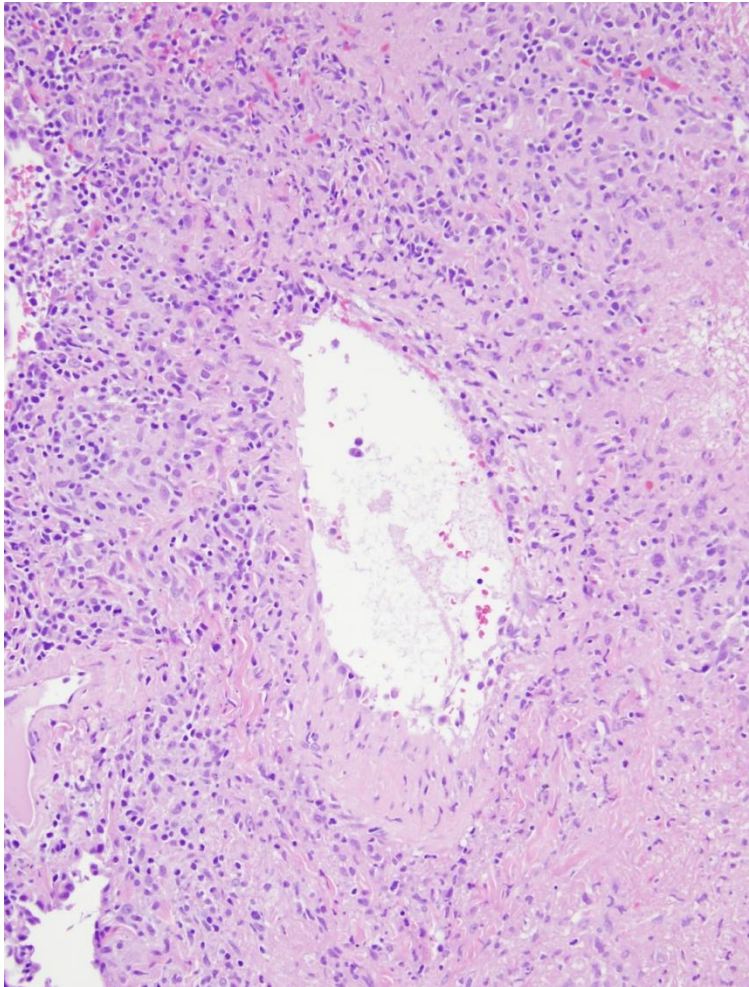
# Lymphomatoid Granulomatosis



Polymorphic Lymphoid Infiltrate

*Courtesy of J.L. Myers*

# Lymphomatoid Granulomatosis



Angiitis – Vascular Infiltration

*Courtesy of J.L. Myers*

# Lymphomatoid Granulomatosis



..... “granulomatosis” consists of foci of necrosis

Liebow et al. 1972

*Courtesy of J.L. Myers*

# Lymphomatoid Granulomatosis

## Liebow et al. 1972 Definition

“ . . . an **angiocentric** and  
angiodestructive **lympho**reticular  
**proliferative** and granulomatous disease  
involving predominantly the lungs.”

# Lymphomatoid Granulomatosis

## Liebow et al. 1972 Definition

“There will undoubtedly be controversy as to whether lymphomatoid granulomatosis with its rather constant histological and radiological features should be considered as **lymphoma**”

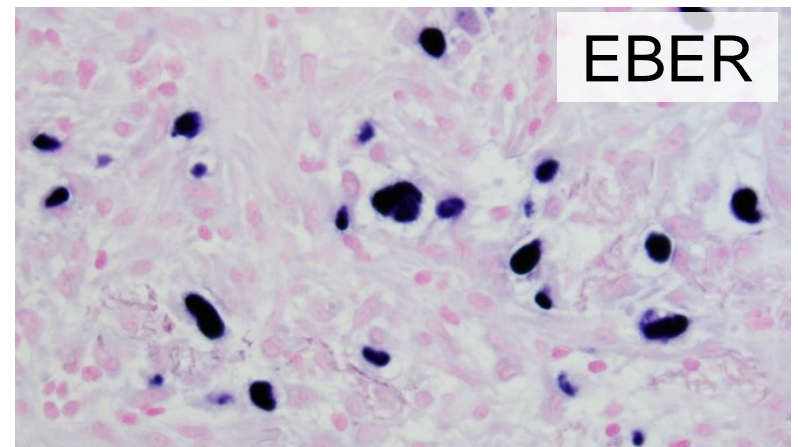
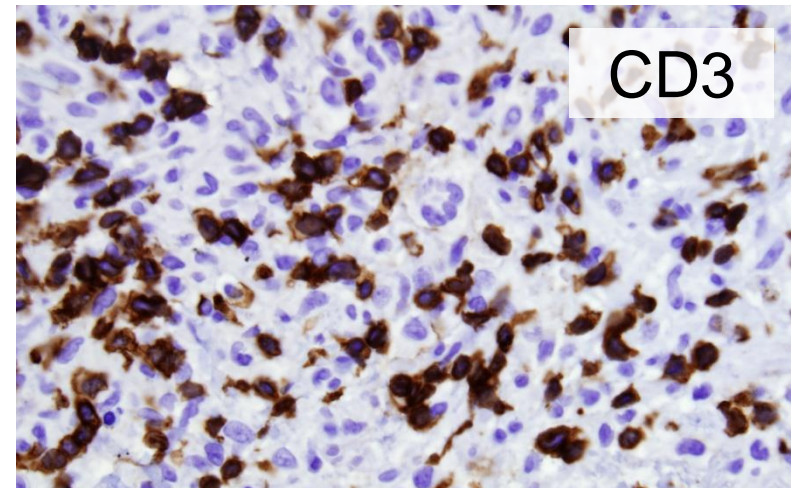
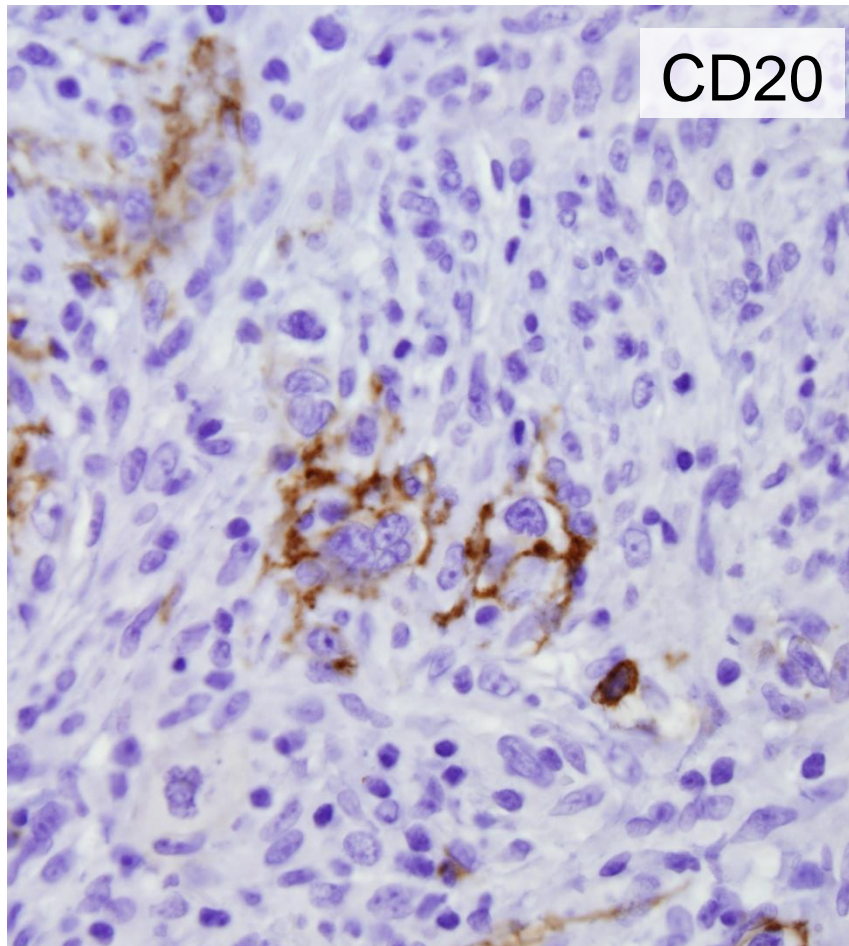
# Lymphomatoid Granulomatosis

## WHO 2008 Definition

“...an **angiocentric** and **angiodestructive lymphoproliferative disease** involving extranodal sites, composed of Epstein-Barr virus (EBV)-positive B cells admixed with reactive T cells, which usually predominate”

†Swerdlow et al (Eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC: Lyon 2008.

# Lymphomatoid Granulomatosis (WHO 2008)

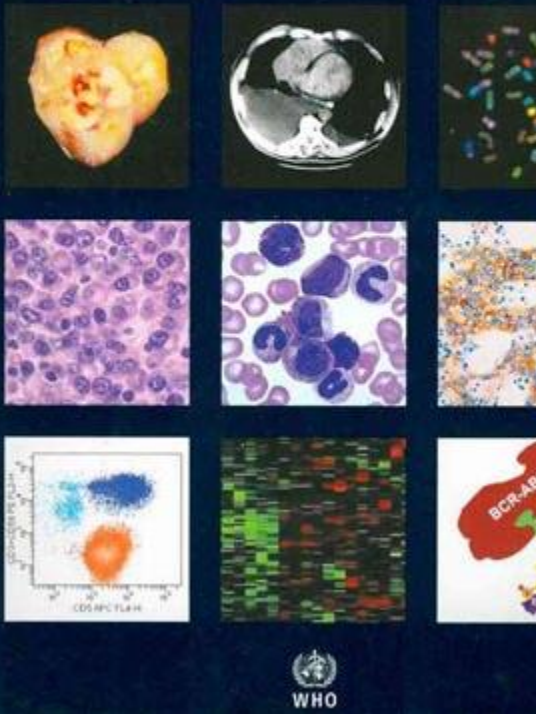


Large atypical cells = EBV/CD20-positive

# Lymphomatoid Granulomatosis (WHO 2008)

## WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine  
Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman



## MATURE B-CELL NEOPLASMS

|  |        |
|--|--------|
| Diffuse large B-cell lymphoma (DLBCL), NOS         | 9680/3 |
| T-cell/histiocyte rich large B-cell lymphoma       | 9688/3 |
| Primary DLBCL of the CNS                           | 9680/3 |
| Primary cutaneous DLBCL, leg type                  | 9680/3 |
| <i>EBV positive DLBCL of the elderly</i>           | 9680/3 |
| DLBCL associated with chronic inflammation         | 9680/3 |
| Lymphomatoid granulomatosis                        | 9766/1 |
| Primary mediastinal (thymic) large B-cell lymphoma | 9679/3 |
| Intravascular large B-cell lymphoma                | 9712/3 |

# Lymphomatoid Granulomatosis

## Outcomes

- 172 (of 283) = 61% dead of disease
- Survival 5.4 – 23 months
- Adverse prognostic factors included
  - Neurologic manifestations
  - *large numbers of atypical lymphoreticular cells within the pulmonary infiltrate*

†summarized in Katzenstein et al. Am J Surg Pathol 2010; 34: e35-e48.

# Lymphomatoid Granulomatosis: Grading

- **Grade 1:** polymorphous lymphoid infiltrate without cytologic atypia. Large transformed lymphoid cells absent or rare. Necrosis, when present, focal. EBV-positive cells <5 /HPF
- **Grade 2:** occasional large lymphoid cells or immunoblasts in a polymorphous background. Necrosis more common. EBV-positive cells 5-50 /HPF
- **Grade 3:** still an inflammatory background, readily identified large atypical B cells, at times in clusters, CD20 positive. Markedly pleomorphic and Hodgkin-like cells often present - necrosis usually extensive. EBV-positive cells >50/HPF

“Any recommendation regarding the value or importance of grading in LYG is, at best, a weak recommendation based on low quality evidence!”

Jeffrey Myers (personal communication)

# NOT Lymphomatoid Granulomatosis

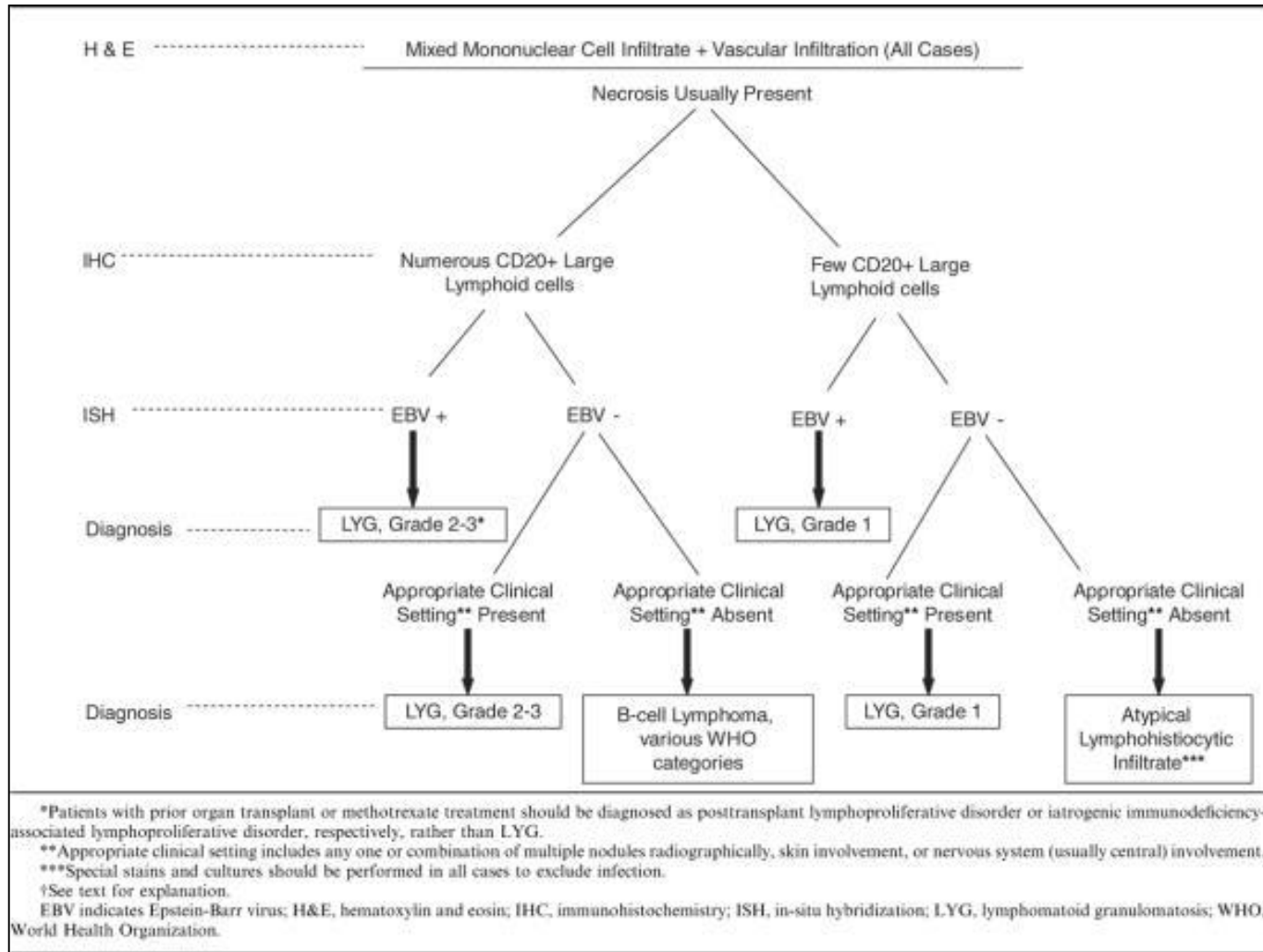
“A uniform population of large atypical EBV-positive B cells without a polymorphous background should be classified as diffuse large B-cell lymphoma, and is beyond the spectrum of lymphomatoid granulomatosis as currently defined.”

Swerdlow et al (Eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC: Lyon 2008.

# Lymphomatoid Granulomatosis: Insights Gained Over 4 Decades.

Katzenstein AI et al Am J Surg Path 2010; 34:e35-e48

TABLE 3 . Algorithm for Diagnosing LYG+



# Lymphomatoid Granulomatosis

## Take Home Message

- A form of malignant lymphoma, in most cases an EBV-related large B-cell lymphoma, admixed with reactive T cells
- As other EBV-related lymphoproliferative conditions in immunocompromised patients, there are implications regarding pathogenesis and treatment

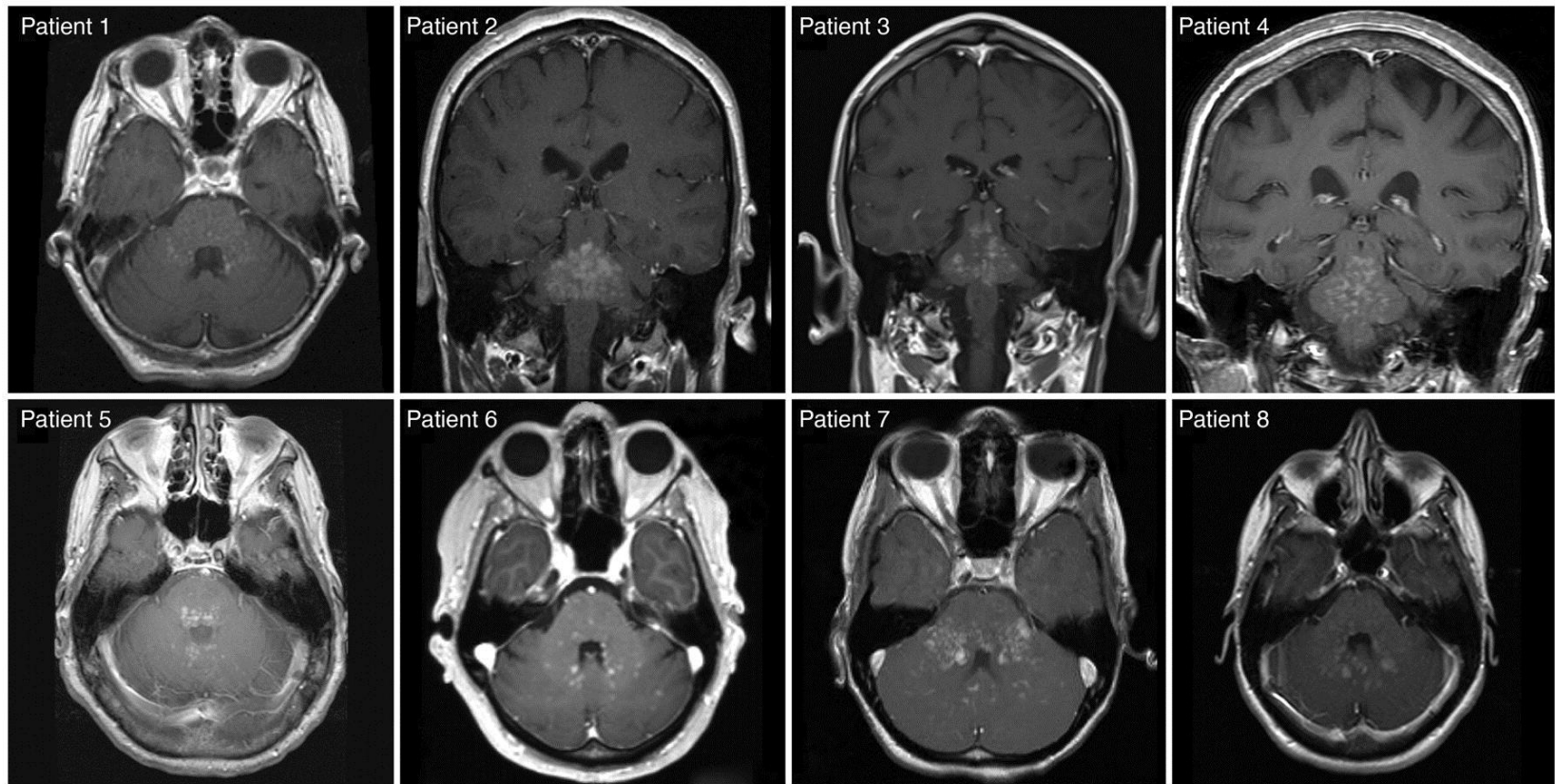
# CLIPPERS

A Chronic Inflammatory CNS Disease & A Challenging  
Acronym

# Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)

- Clinical syndrome with facial paresthesias, diplopia, gait ataxia, dysgeusia, and myelopathy
- Distinct imaging with punctate, curvilinear, perivascular gadolinium enhancement centered in the pons
- Exquisitely responsive to high-dose corticosteroid therapy - often with recurrence or “relapse” of the inflammatory process on discontinuing or tapering of the corticosteroid therapy

# MRI characteristics of CLIPPERS syndrome - pontine-predominant

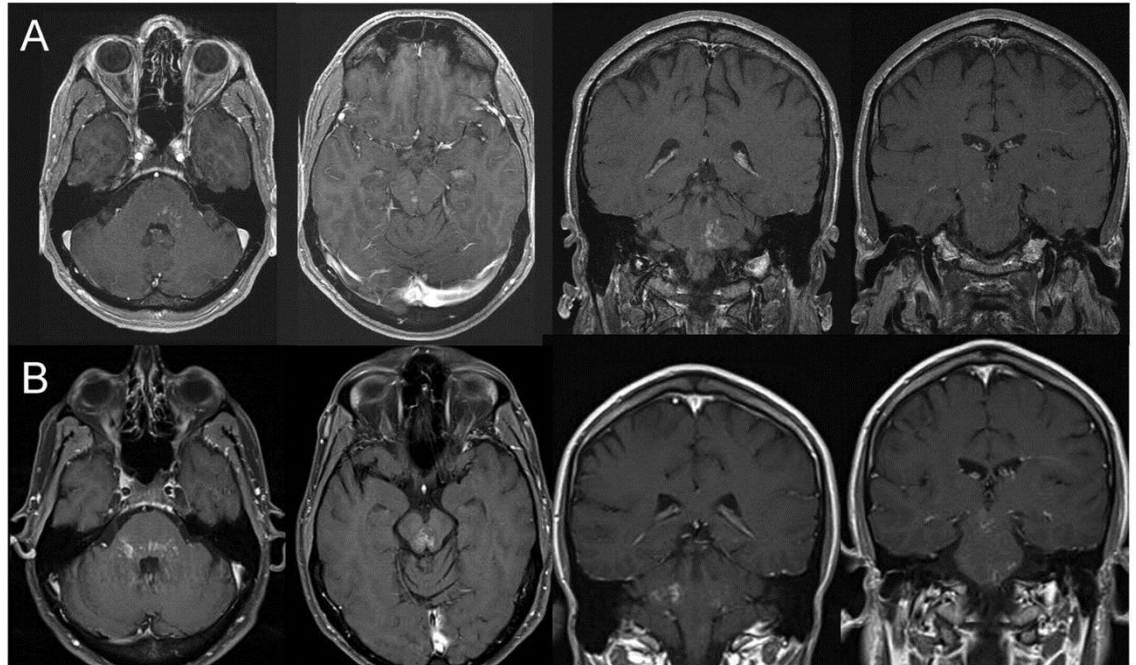


Sean J. Pittock et al. *Brain* 2010;133:2626-2634

**Representative MRI findings outside  
of primary brainstem abnormalities.**

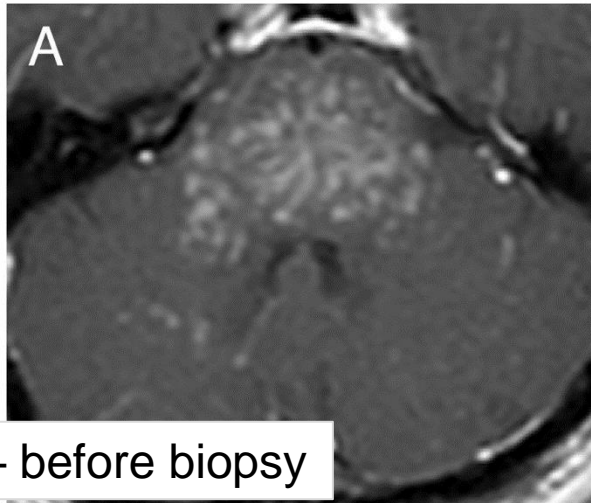


**Progression of lesions over 6 months in Patient 3.**

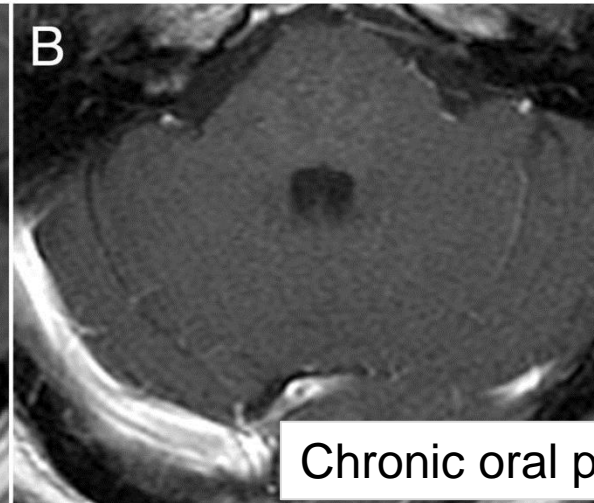


Sean J. Pittock et al. Brain 2010;133:2626-2634

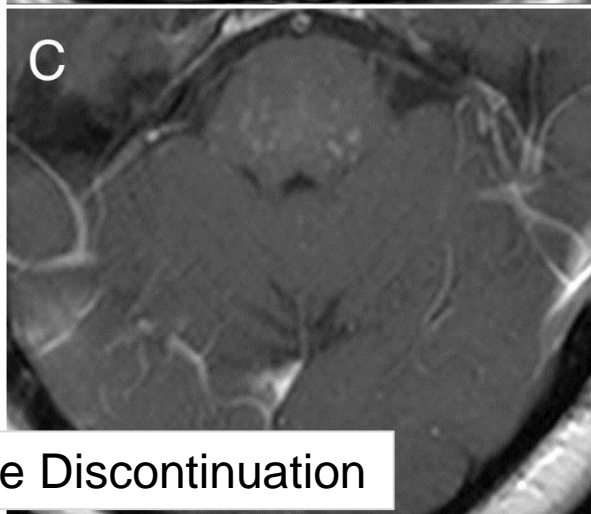
# Marked reduction in extent of gadolinium enhancement following immunotherapy in Patient 2.



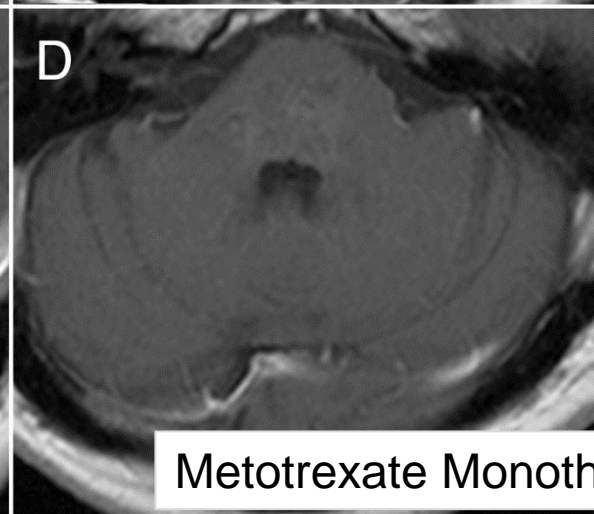
Off therapy – before biopsy



Chronic oral prednisone



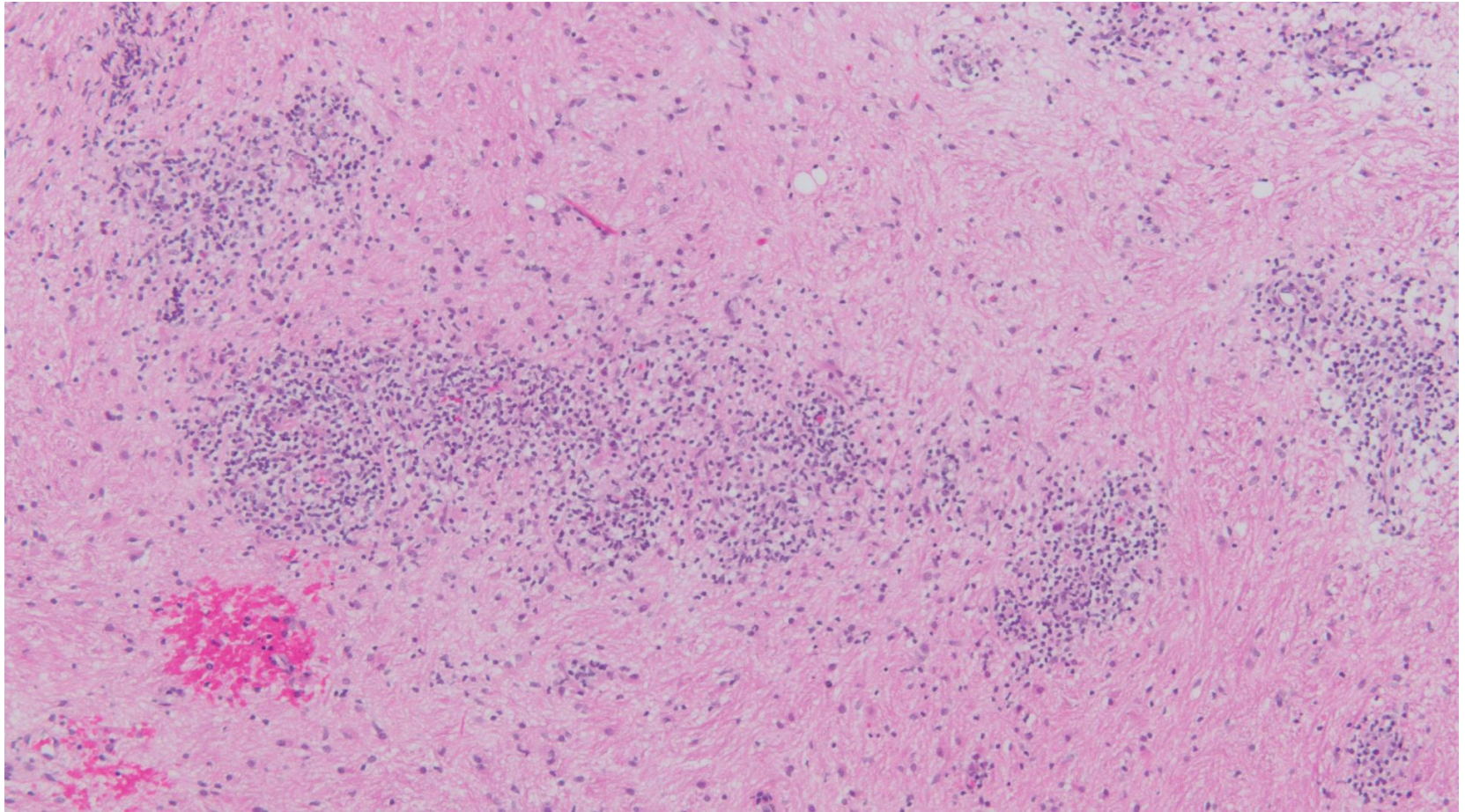
After Prednisone Discontinuation



Metotrexate Monotherapy 1.5 years

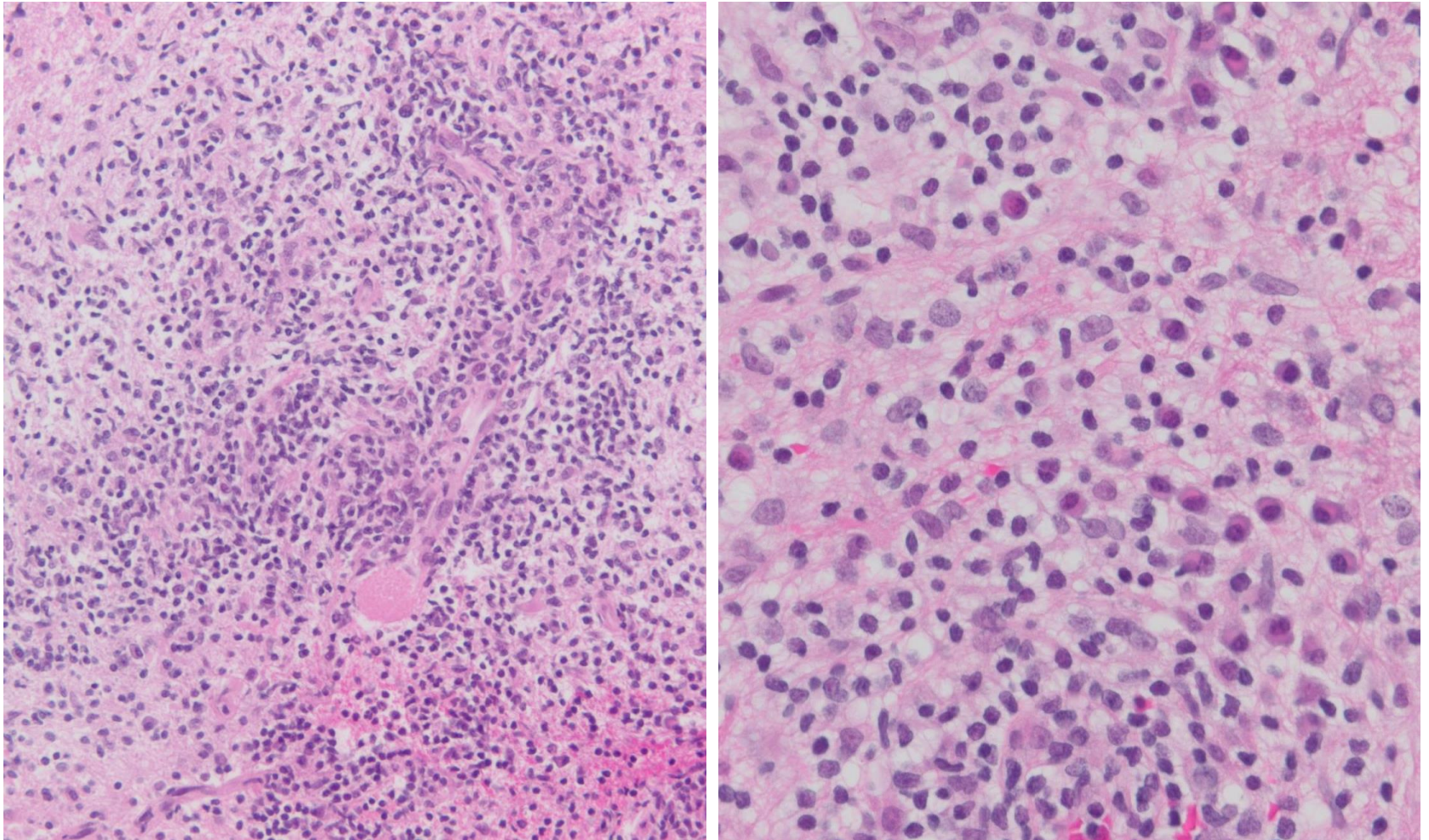
Sean J. Pittock et al. *Brain* 2010;133:2626-2634

# CLIPPERS: Pathology



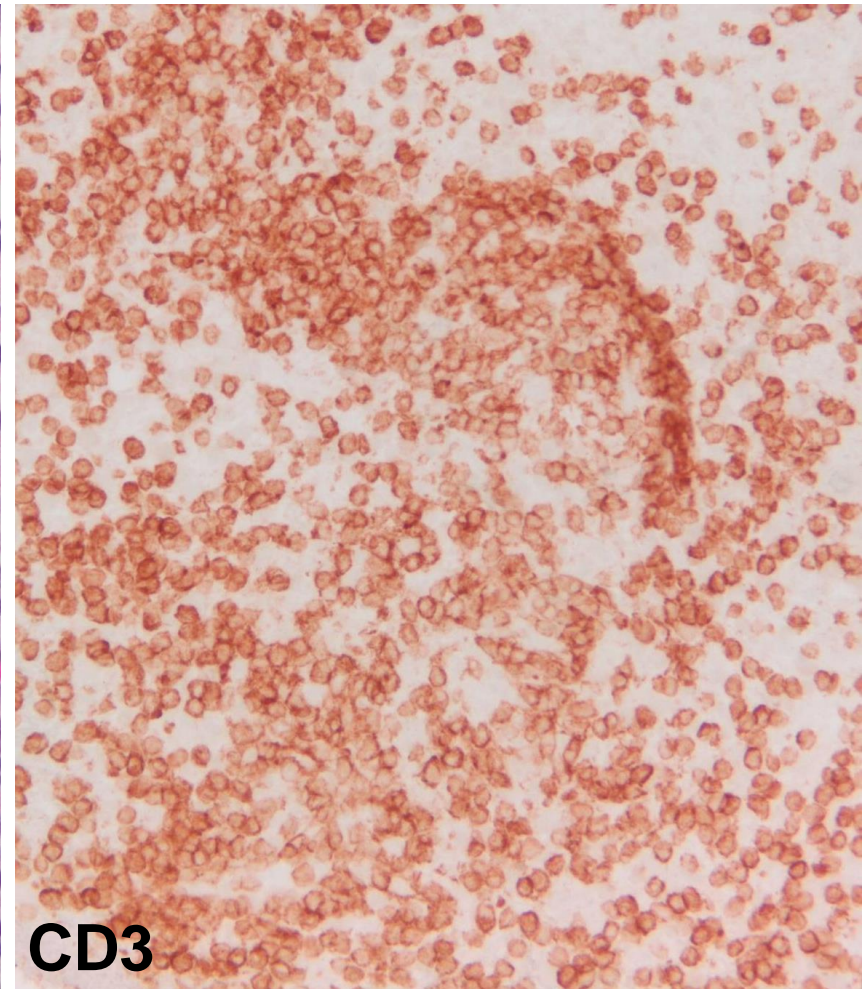
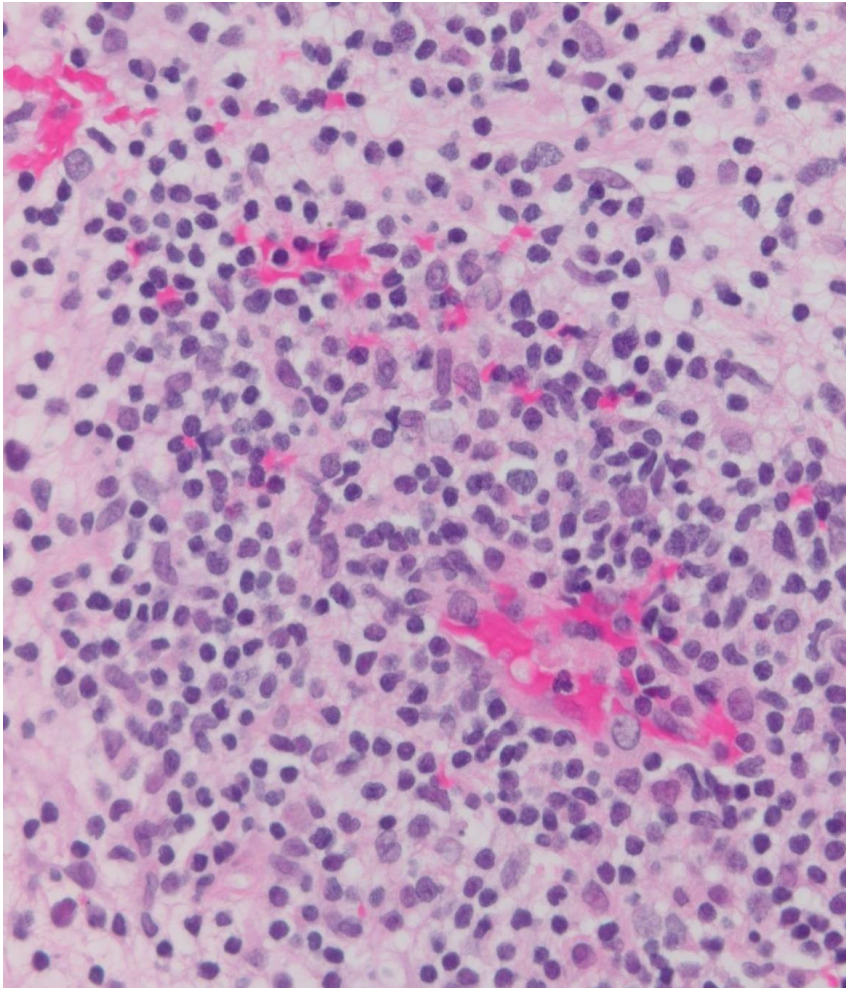
- Chronic lymphocytic infiltrate without “parenchymal damage”

# CLIPPERS: Pathology



- Perivascular and Parenchymal – Not typical of Vasculitis

# CLIPPERS: Pathology



- T-cell–predominant infiltrate

# CLIPPERS: Differential Diagnosis

- CNS lymphoma, Glioma, Lymphomatoid granulomatosis
- CNS vasculitis, Bickerstaff encephalitis, Paraneoplastic disease
- Infectious (tuberculosis, neurosyphilis, Whipple's disease, parasitic infection)
- CNS demyelinating disease, Behçet's, Langerhans cell histiocytosis, Erdheim-Chester disease

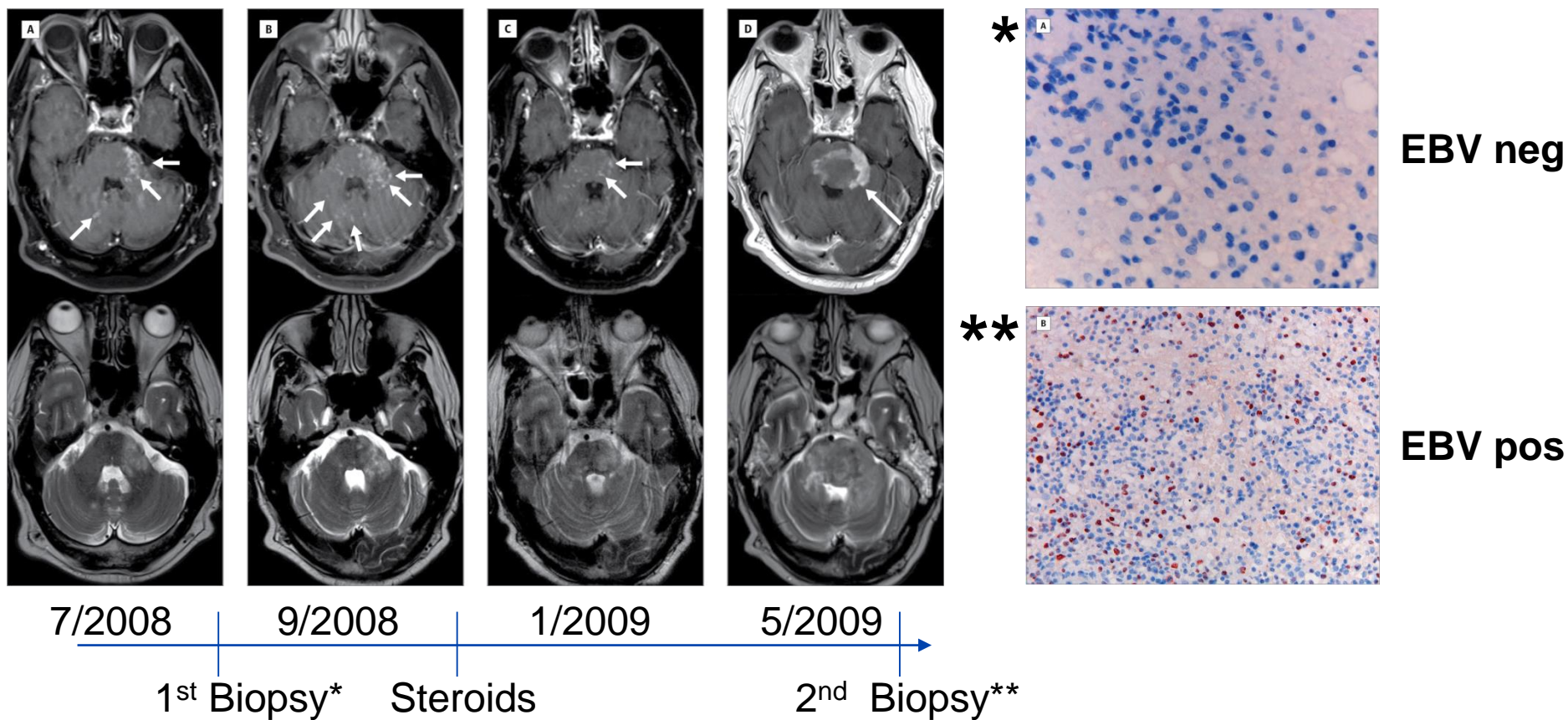
*All these possibilities were excluded*

# To my surprise

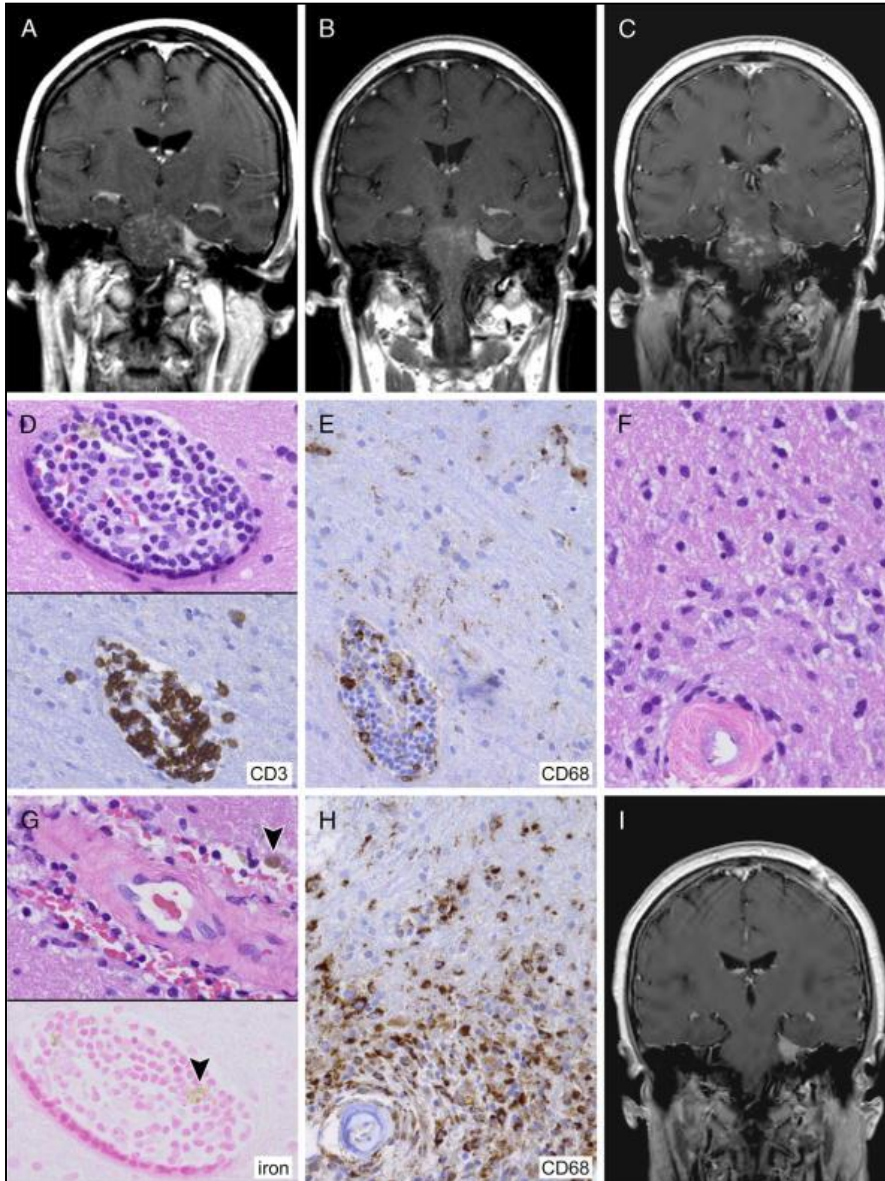
- Over 30 papers have been published regarding CLIPPERS (6/6/2015)
- The phenotype has expanded emphasizing wider manifestations and overlap with CNS lymphoma, CNS vasculitis, MS and other conditions
- Intense debate has developed: is it a disease or a syndrome?

From: **Fatal B-cell Lymphoma Following Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive to Steroids**

JAMA Neurol. 2013;70(7):915-918. doi:10.1001/jamaneurol.2013.2016



# FIGURE 1



## CLIPPERS With Chronic Small Vessel Damage: More Overlap With Small Vessel Vasculitis?.

Kleinschmidt-DeMasters, Bette; West, Matthew

Journal of Neuropathology & Experimental Neurology. 73(3):262-267, March 2014.

DOI: 10.1097/NEN.0000000000000050

FIGURE 1 . (A) Magnetic resonance imaging (MRI) with gadolinium at time of clinical presentation shows curvilinear and speckled contrast enhancement symmetrically distributed in pons and radiographically typical for CLIPPERS. Note the incidental left cerebellopontine angle mass. (B) MRI with gadolinium after first round of steroids shows significant resolution of the neuroimaging abnormalities; the patient was also significantly clinically improved at this time. (C) MRI with gadolinium at the time of clinical relapse of symptoms several months after her steroid taper shows recurrence of the pontine abnormalities. (D) Brain biopsy showed multifocal white matter small vessels with perivascular and vascular wall inflammation composed of small lymphocytes without cytologic atypia (top; hematoxylin and eosin, original magnification, 600x) that were predominantly CD3-positive T-cell lymphocytes (bottom; original magnification, 600x). Individual T cells in parenchyma were also noted. (E) CD68-immunopositive perivascular macrophages and parenchymal microglial cells were present, although no tight microglial clusters were seen (original magnification, 600x). (F) Other vessels showed more chronic injury with hyalinization and minimal inflammation, resulting in fibrosis, particularly of the adventitia (hematoxylin and eosin, original magnification, 600x). (G) Hyalinized small vessels showed scant perivascular pigment (top, arrowhead), which was negative for iron (bottom; Perl iron stain, arrowhead, original magnification, both 600x). (H) Chronically injured hyalinized small vessels showed surrounding increased concentrations of macrophages but no cavitation or extensive demyelination (immunostaining for CD68 with light hematoxylin counterstain, original magnification, 400x). (I) After cyclophosphamide, CellCept, and prednisone treatment a second time, her neuroimaging and clinical abnormalities regressed, as seen on MRI with gadolinium.

# Diagnosis of CLIPPERS

- Clinical and radiological characteristics
  - Punctate, curvilinear, perivascular gadolinium enhancement peppering the pons
- There is no specific serum biomarker:
  - Its nosological position is still to be established
  - One should be careful in diagnosing CLIPPERS, especially if the clinical and radiological features are atypical
- As a neuropathologist:
  - Be aware of the wide differential diagnosis
  - Pathology is “characteristic, but not specific”

## In Summary

- Primary CNS lymphoma
- Lymphoma in disguise:
  - Vanishing Lymphoma
  - Sentinel lesions
- Immunodeficiency/EBV associated lymphoma
  - Lymphomatoid Granulomatosis
- CLIPPERS



Thank you!