Inflammatory disease of the Meninges in Surgical Neuropathology

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Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

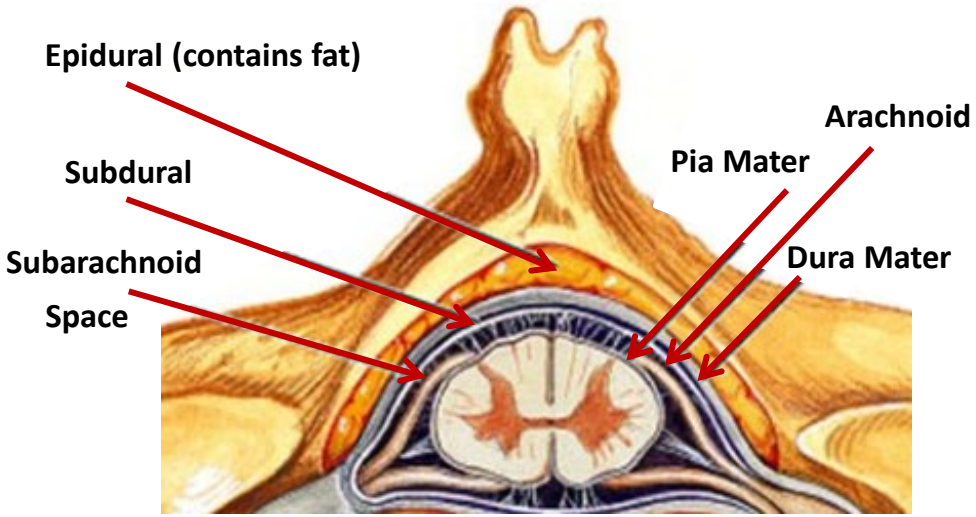
- Describe the basic structure of the meninges and the nomenclature of the pathological processes occurring in the meninges
- Identify common inflammatory conditions which can be encountered in surgical meningeal biopsies
- List criteria supportive and against the diagnosis of meningeal IgG4-related disease

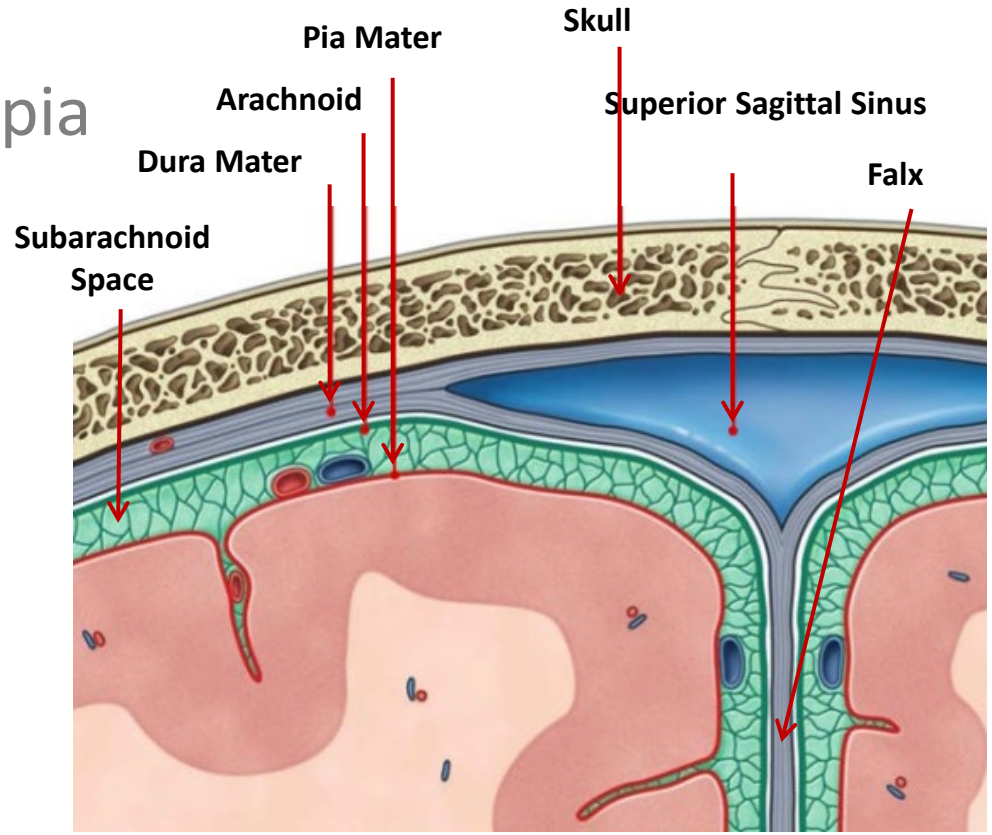
Outline

- Focused discussion of meningeal pathological processes
  - From a Surgical Pathology point of view
  - “meningeal enhancement”
- Inflammatory Meningeal Diseases:
  - IgG4-related disease Infectious
  - Other inflammatory disorders (including sarcoid, granulomatosis with polyangiitis, rheumatoid arthritis)
  - Infectious diseases

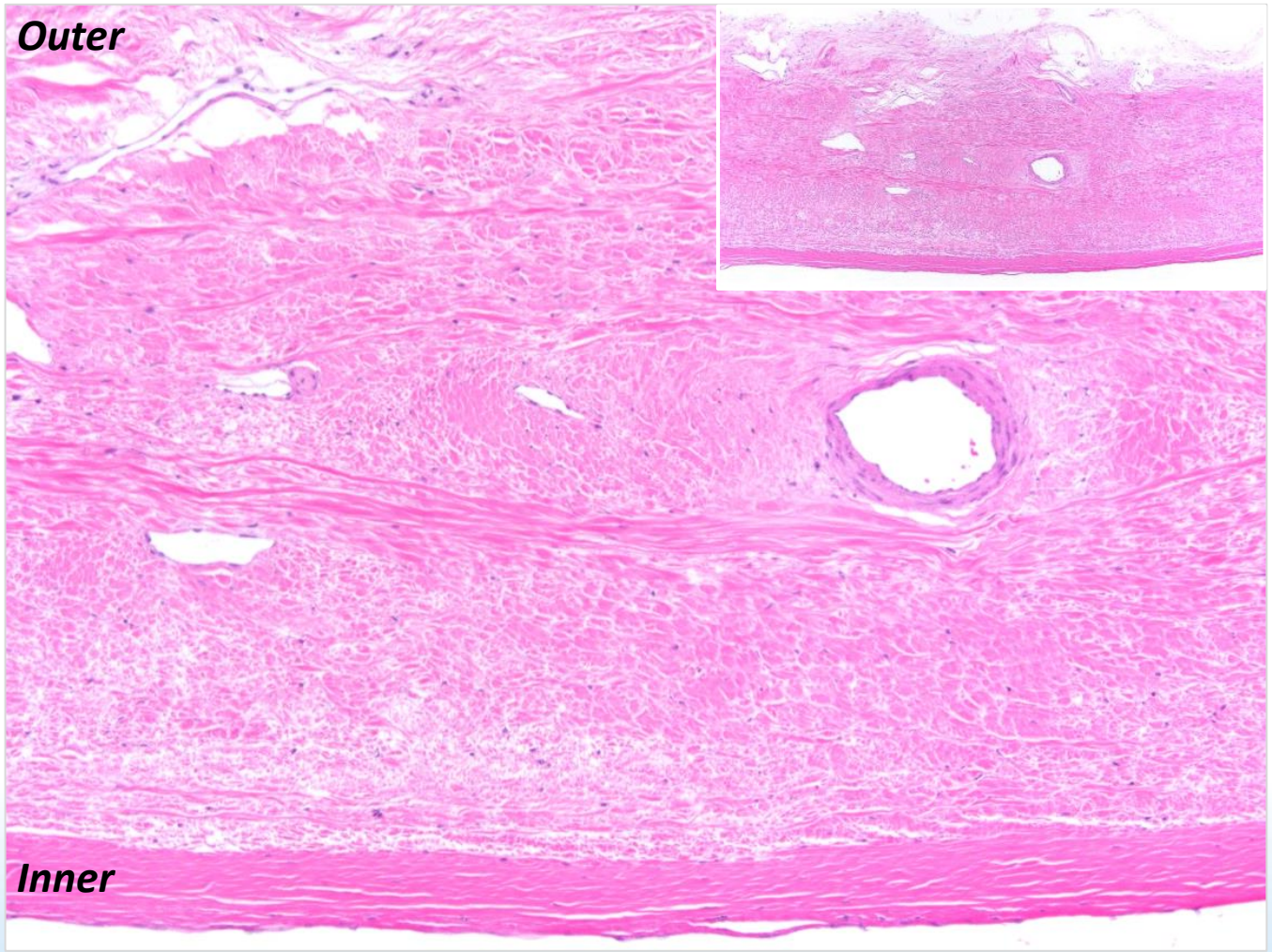
Meningeal Disease

- Pachymeninges (“thick”) = dura mater
- Leptomeninges (“thin”) = arachnoid & pia

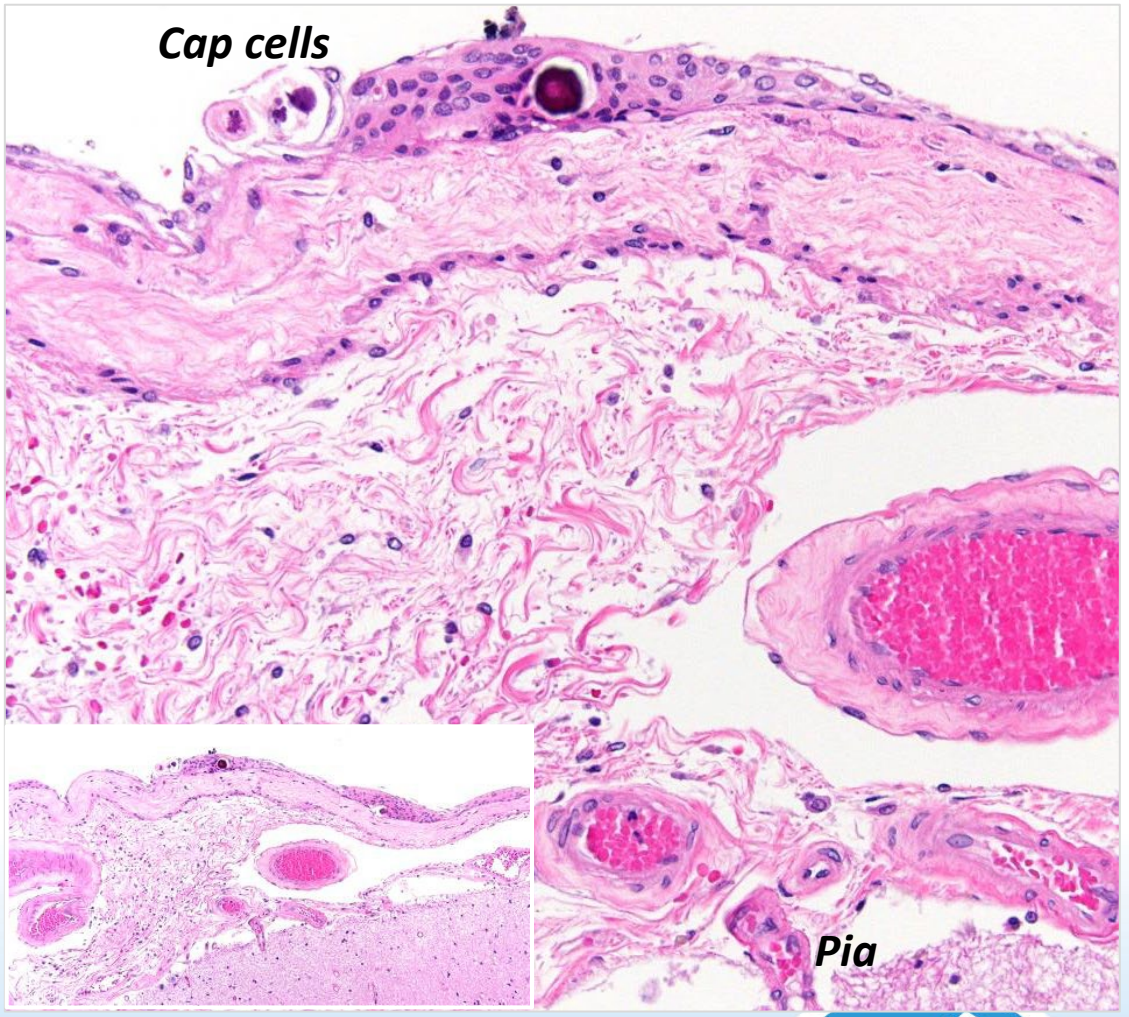




Dura



Arachnoid



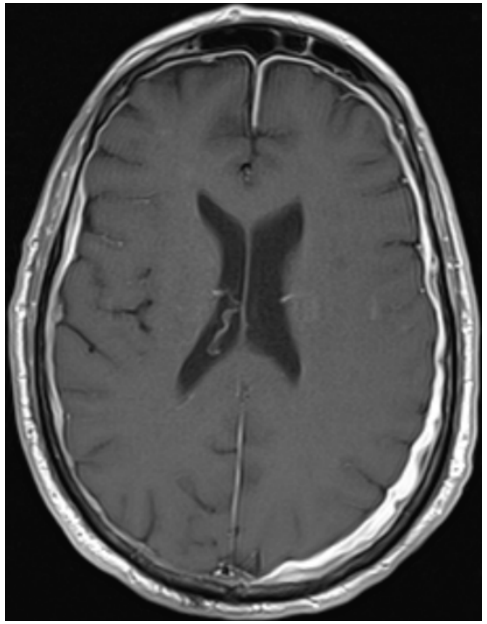
Meningeal Inflammatory/Infectious Diseases

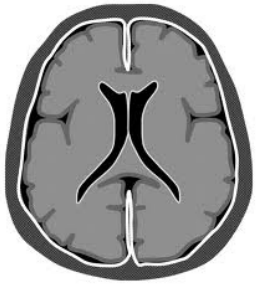
Agent	Site	Type	Diagnosis

• Viral
• Bacterial
• Parasitic (Protozoan)
• Fungal
	• Epidural Space
	• Subdural Space
	• Meninges
	  • Pia & Arachnoid
	  • Dura
		• Acute
		• Subacute
		• Chronic
			• Epidural Abscess
			• Subdural Empyema
			• Meningitis
			  • Leptomeningitis
			  • Pachymeningitis

Inflammatory Meningeal Disease Nomenclature

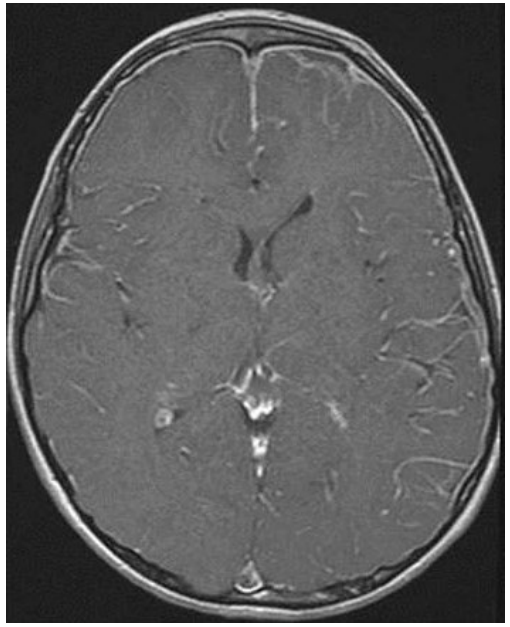
Pachymeningitis

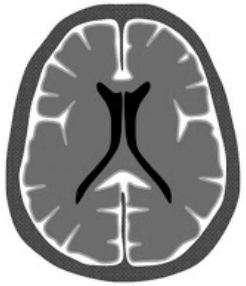




Dural involvement, typically with thickened enhancing pachymeninges

Leptomeningitis



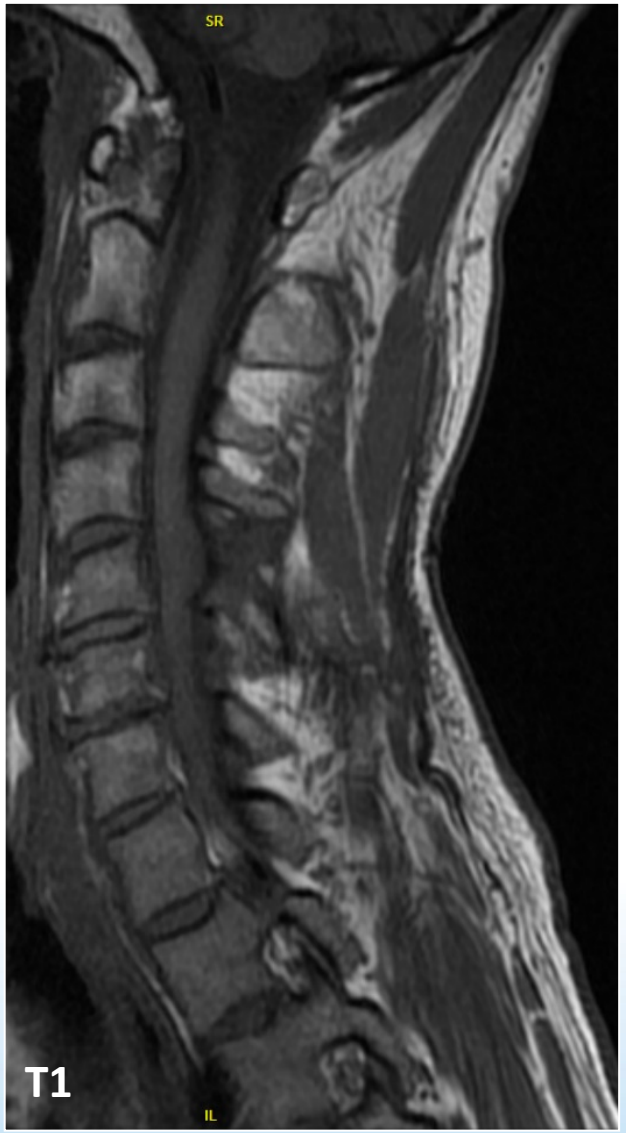


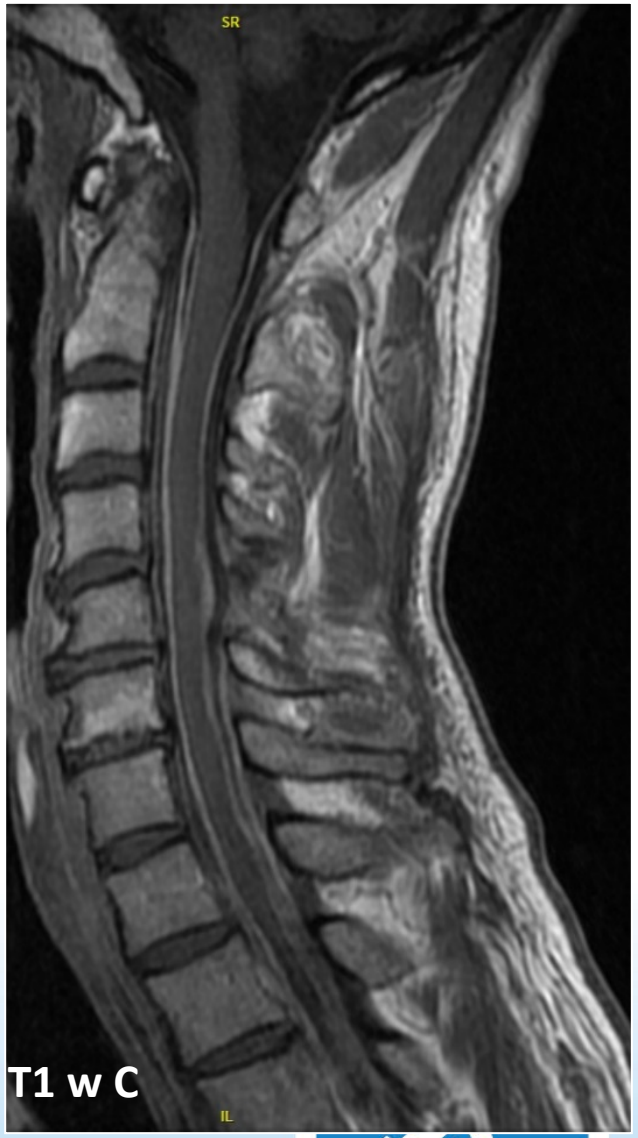
Leptomeningeal involvement, with enhancement which follows sulci

"Hypertrophic meningitis" refers to the robust thickening of the meninges, diffuse or nodular

Case Presentation

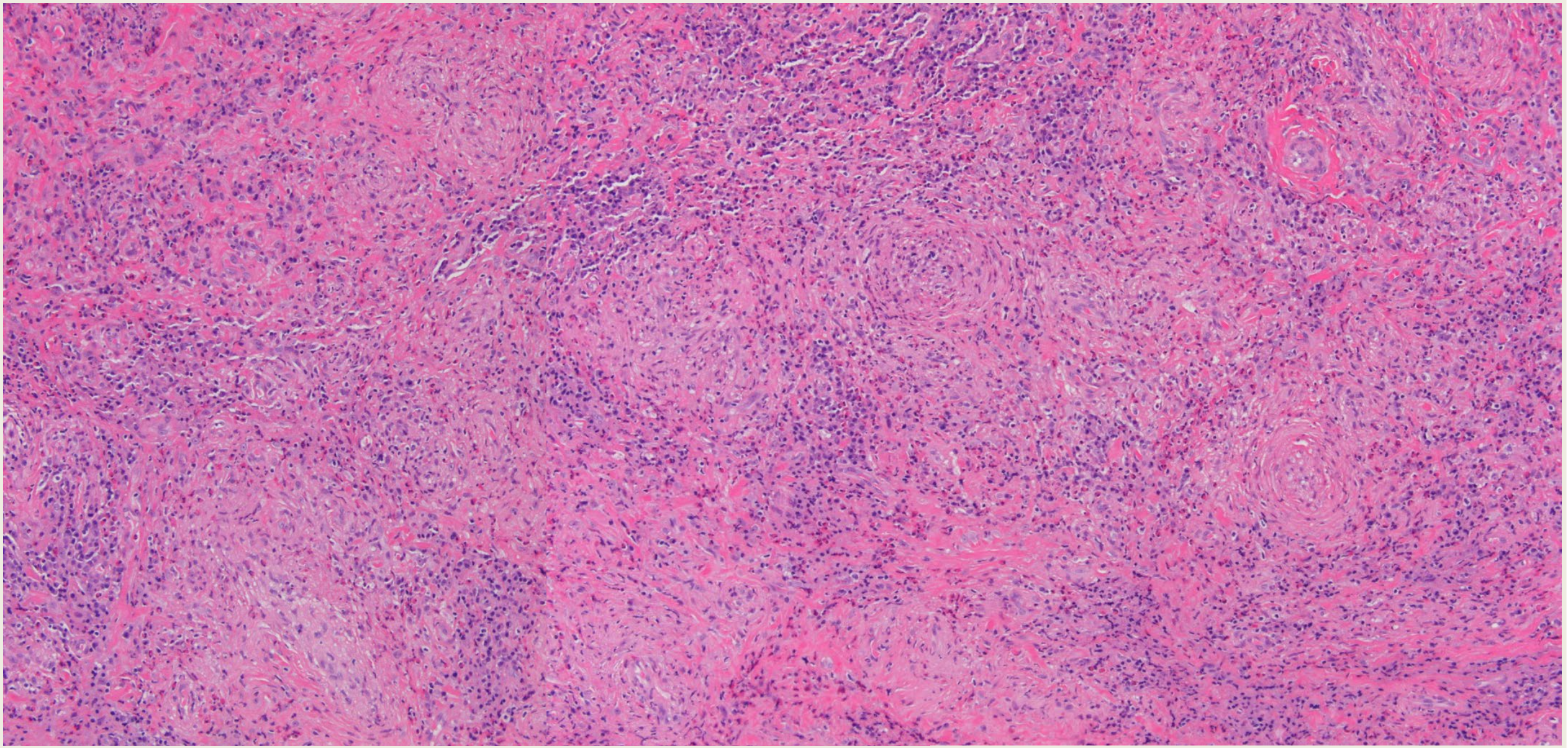
- 52-year-old man with a 24-mo history:
  - “C5 fracture“ after a fall
  - Developed neck pain, which became severe & persistent (6 mo)
  - Developed tingling involving right and left hand - primarily 4^{th} and 5^{th} finger of each hand (3 mo)
  - Developed difficulty opening bottles with his hands (6 mo)
  - Developed leg weakness and gait deterioration (4 mo)

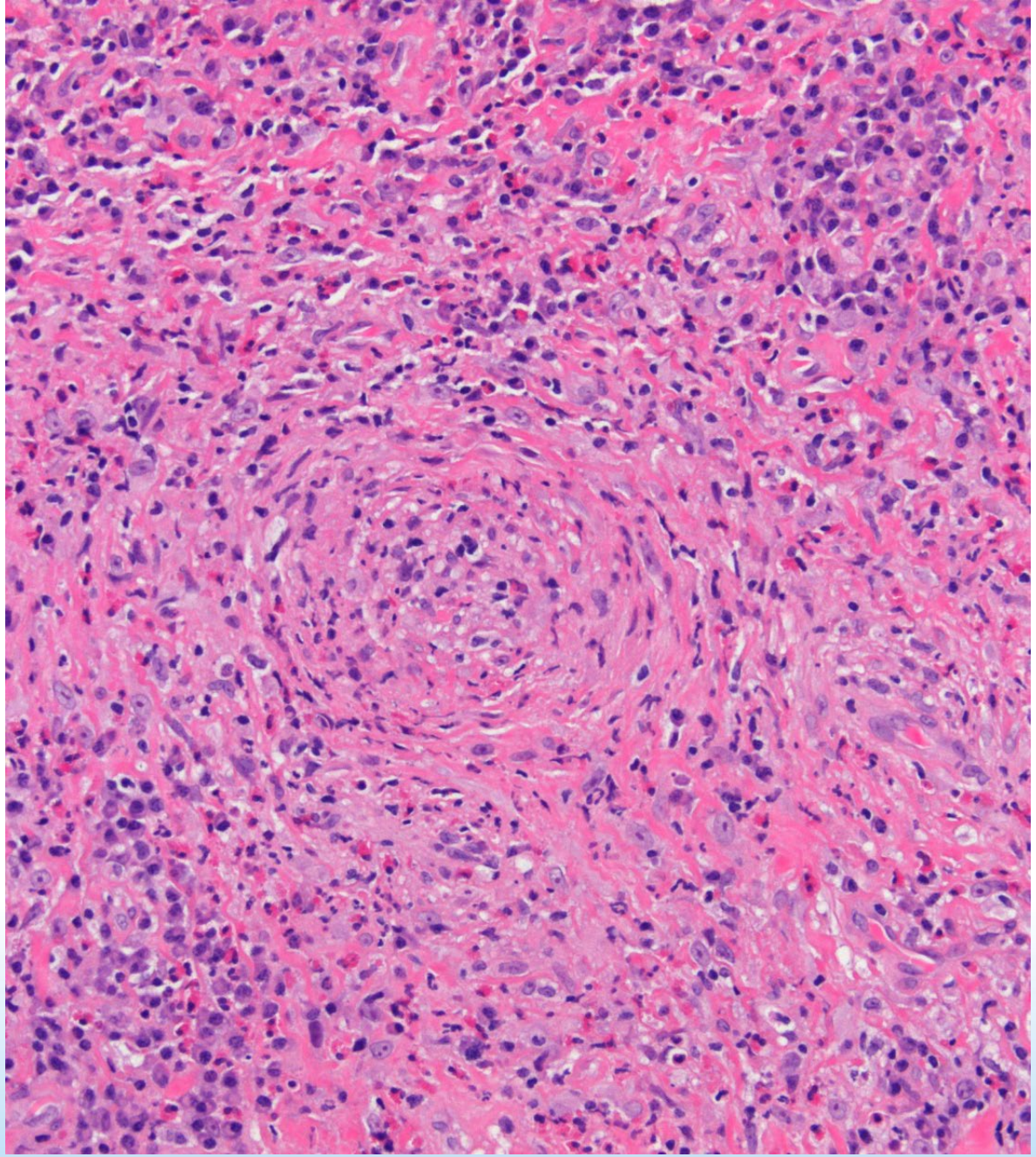


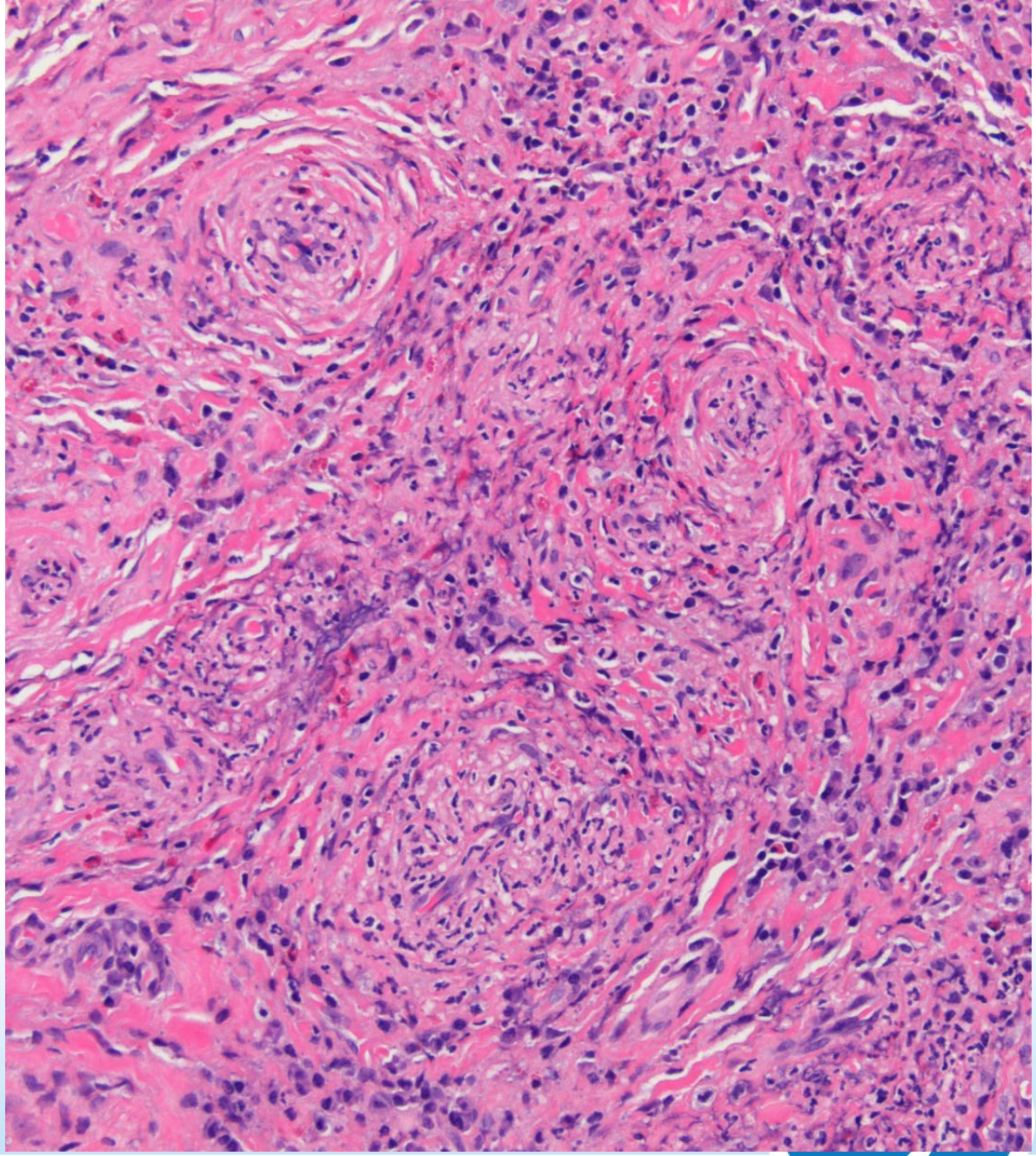


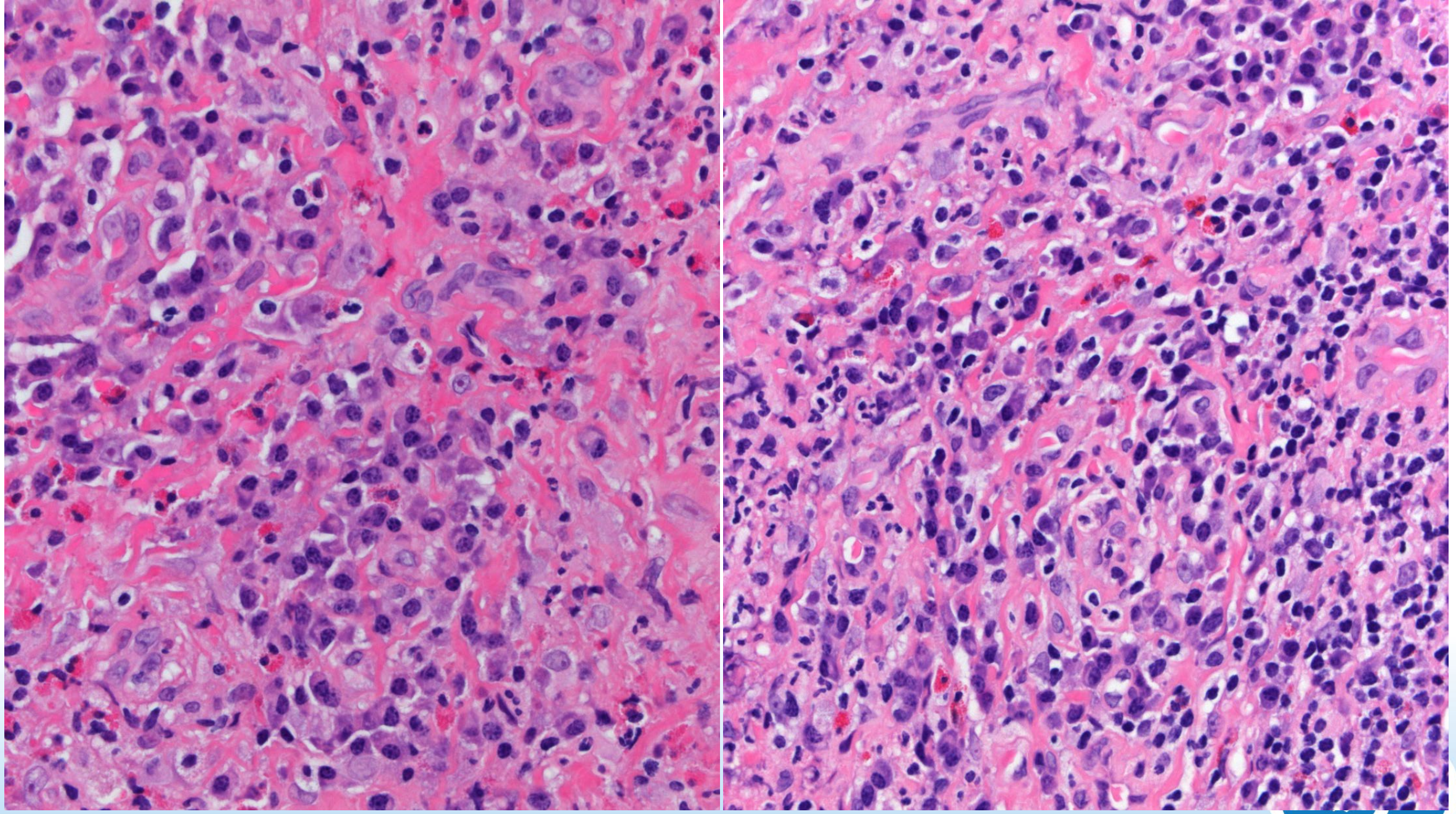
Before you receive the biopsy – Differential diagnosis

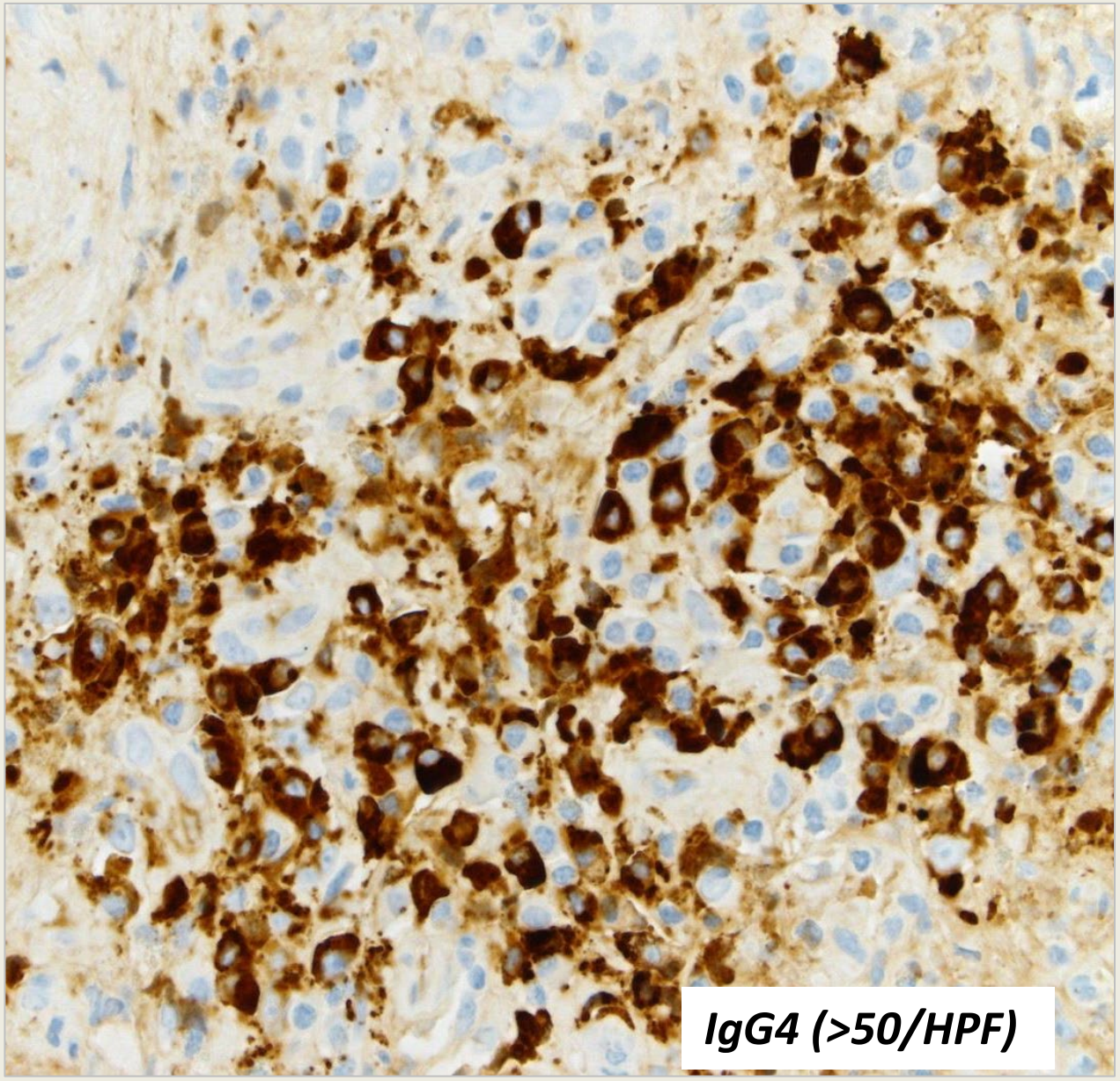
- Infection (bacterial, fungal, other)
- Sarcoid
- IgG4 related disease
- Rheumatoid arthritis
- Lymphoma/leukemia
- Drop or hematogenous metastasis
- Primary diffuse meningeal gliomatosis
- Primary diffuse meningeal melanocytic tumor
- Meningeal enhancement related to CSF hypotension
- Idiopathic pachymeningitis



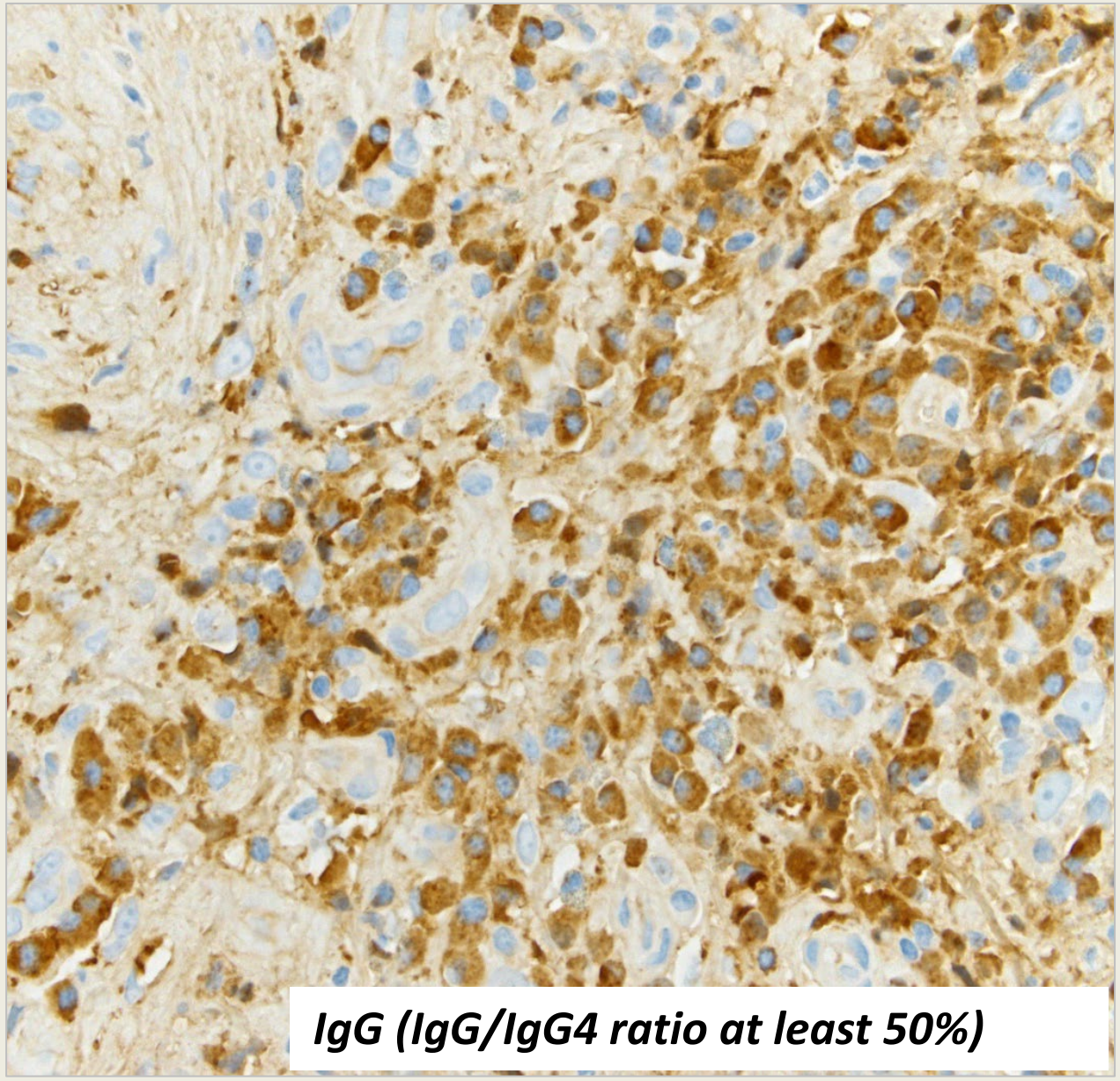








IgG4 (>50/HPF)



IgG (IgG/IgG4 ratio at least 50%)

Diagnosis

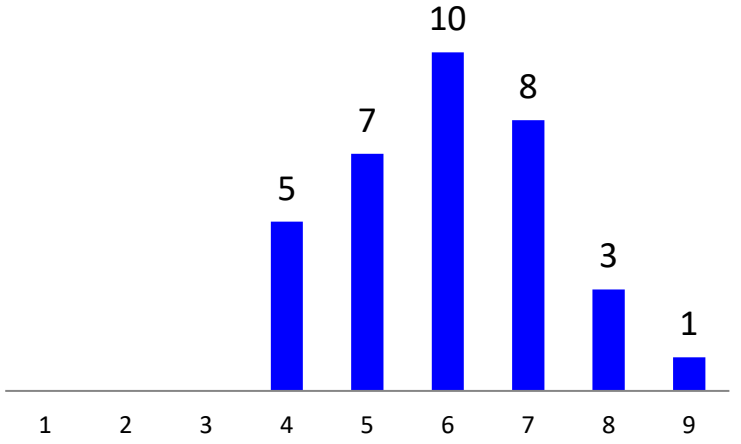
Chronic lymphoplasmacytic inflammation with storiform fibrosis and increased IgG4, consistent with IgG4 related disease

Meningeal IgG4-Related Disease

- Most commonly involves pachymeninges
- Intracranial > spinal
- May involve meninges alone or together with:
  - Adjacent orbital, sinus and brain structures, including pituitary stalk/gland
  - Other organs throughout the body
- Elevated serum IgG4, highly sensitive, specificity around 60%
  - False negative frequent in cases without systemic involvement

Age Distribution by Decade

N=34, 21M - 13F



Male	4	3	6	6	3	1	
Female	1	4	4	2	2	0	

Semin Neurol 2014;34:395-404

Meningeal IgG4-RD Pathogenesis

- Fibrosis results from a non-specific fibroblast activation caused by aberrant immune response to a “still unknown antigen”
- Likely a complex immune response behind IgG4 production, IL-10 mediated, diverting a “classical T-helper type 2 (Th2) response” in favor of IgG4
- IgG4 excess concentration could be regarded as a counter-regulatory mechanism to dampen inflammation rather than the primary driver

Meningeal IgG4-Related Disease:
Diagnostic Histologic Criteria

- Major histologic features associated with IgG4 related disease include:
  - Dense lymphoplasmacytic infiltrate
  - Fibrosis, arranged at least focally in a storiform pattern
  - Obliterative phlebitis
- Increased number of IgG4 + plasma cells (> 10 per HPF)
- Ratio of IgG4+/IgG+ plasma cells >40%
- Combination of at least 2 of the major histologic features with IHC cutoffs for plasma cells are diagnostic of IgG4-related disease

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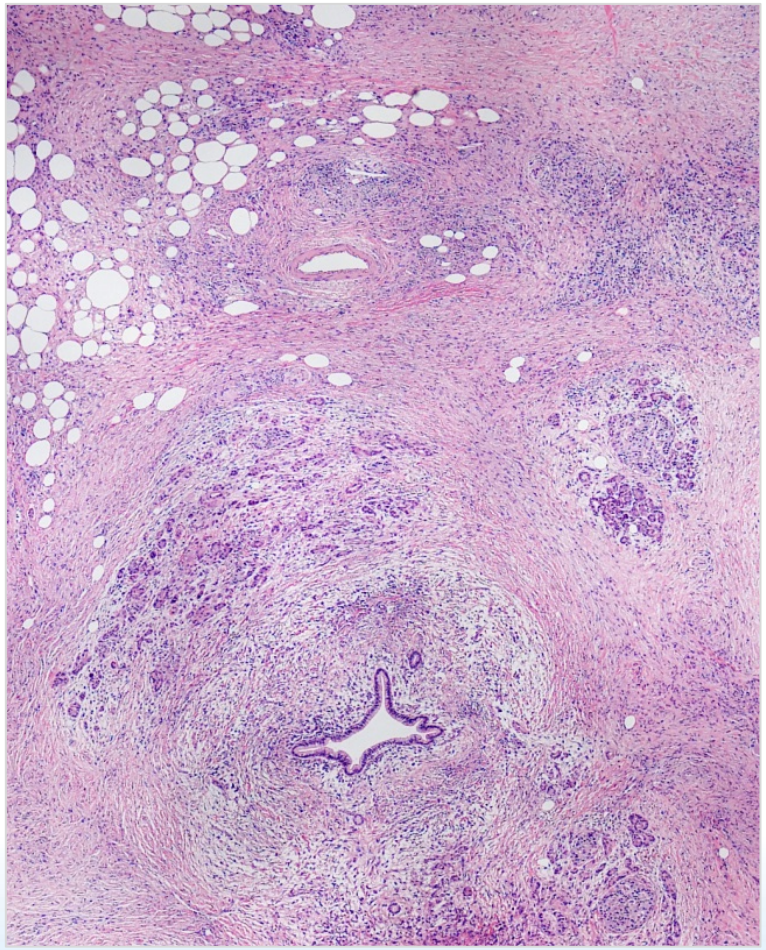
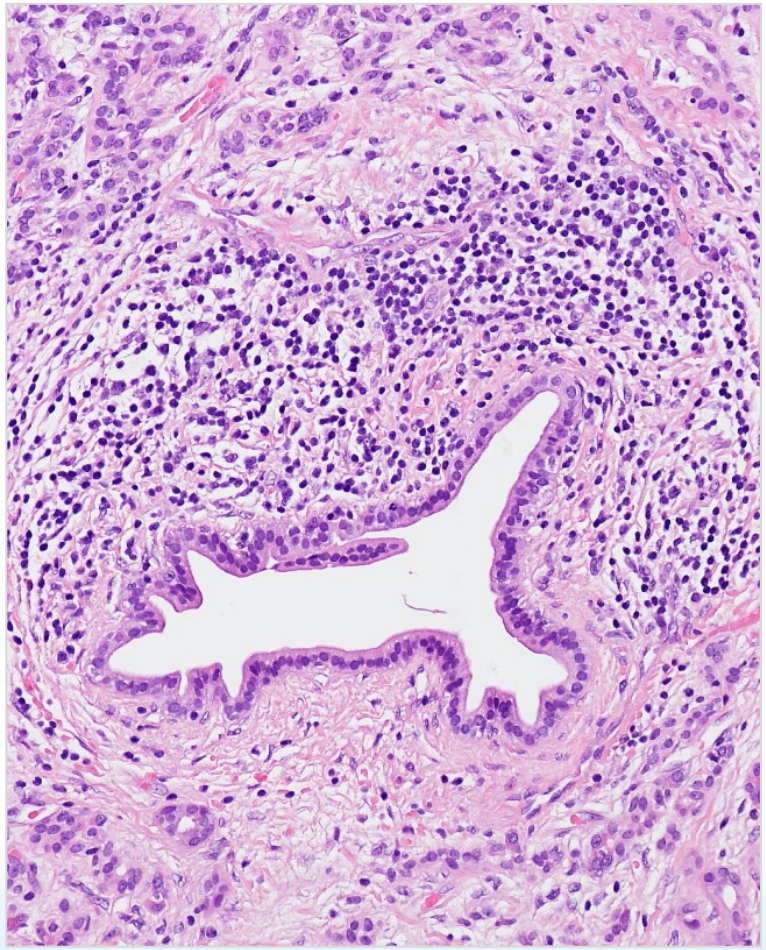
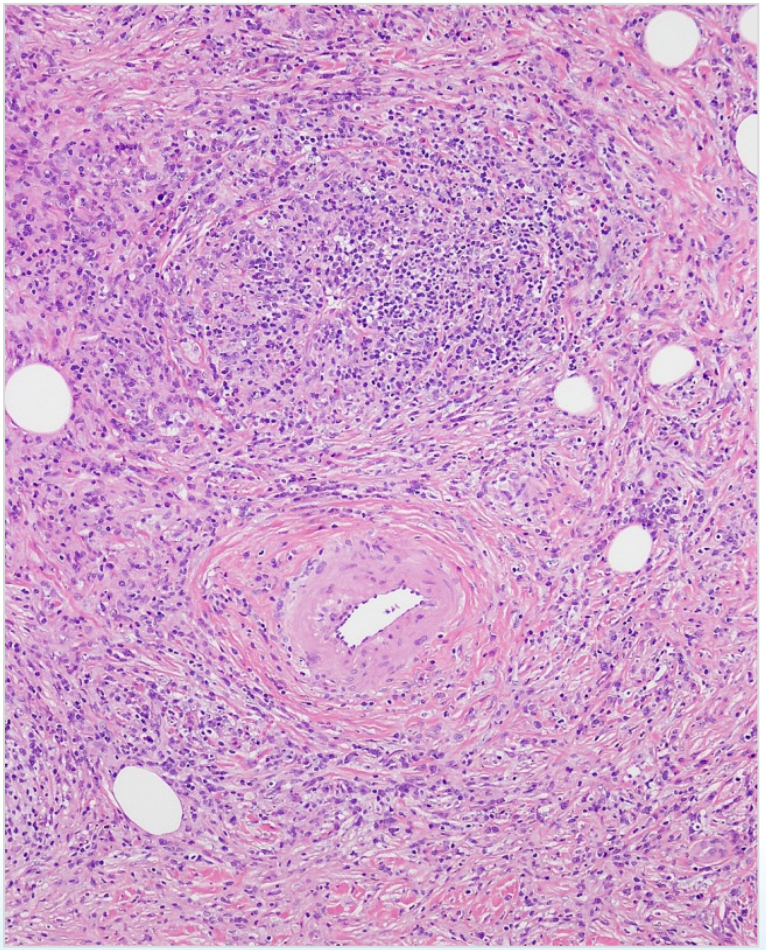
IgG4-related autoimmune pancreatitis



Fibrosis arranged at least focally in a storiform pattern



Dense lymphoplasmacytic infiltrate



Obliterative phlebitis

Variability of histopathology of IgG4-related disease

	Inflammation	Fibrosis	Phlebitis	Others
Lacrimal gland	No unique features	Typical storiform fibrosis is relatively uncommon. More often collagenous fibrosis	Sometimes lacks obliterative phlebitis	
Salivary gland	Often associated with conspicuous lymphoid follicle formation	Storiform fibrosis is rare in parotid and minor salivary glands	Sometimes lacks obliterative phlebitis	
Lymph node	No unique features	Fibrosis is only seen in inflammatory pseudotumor-like lesions	Most often lacks obliterative phlebitis	Five histological patterns*
Lung	Small aggregates of neutrophils may be present in alveolar spaces or within the inflammatory infiltrates	Sometimes lacks storiform fibrosis, particularly in non-solid lesions (eg, interstitial pneumonia)	No unique features	Obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions
Kidney	No unique features	No unique features	Obliterative phlebitis is less common particularly in needle biopsies	

*(1) multicentric Castleman's disease-like, (2) follicular hyperplasia, (3) interfollicular expansion, (4) progressive transformation of germinal center, and (5) nodal inflammatory pseudotumor-like.

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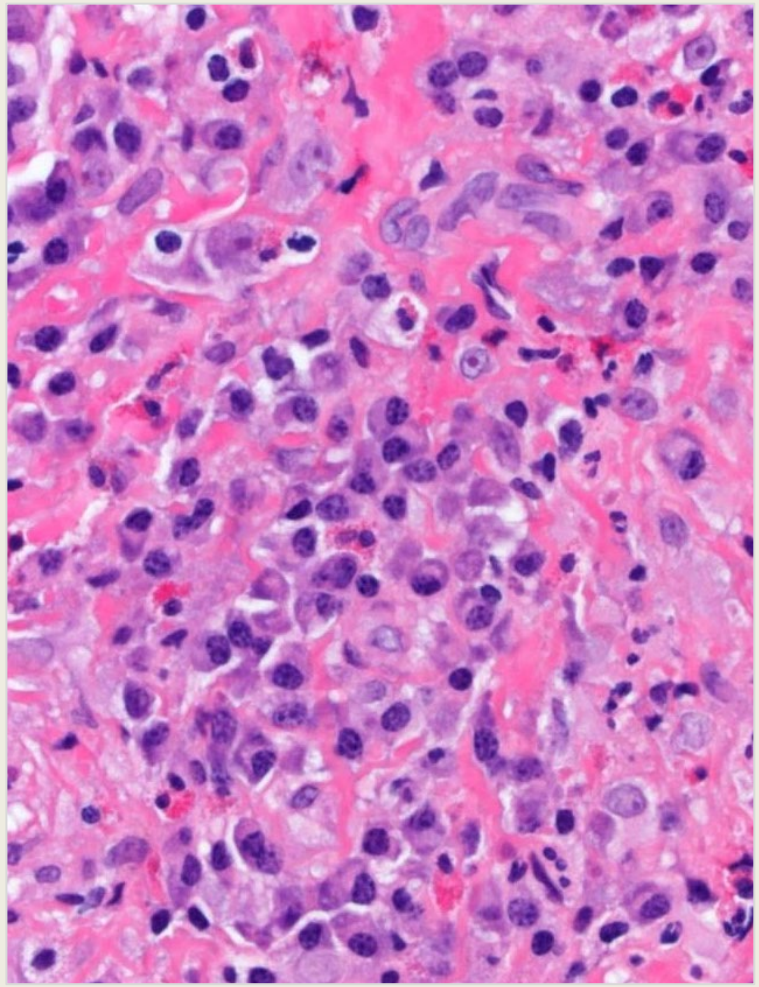
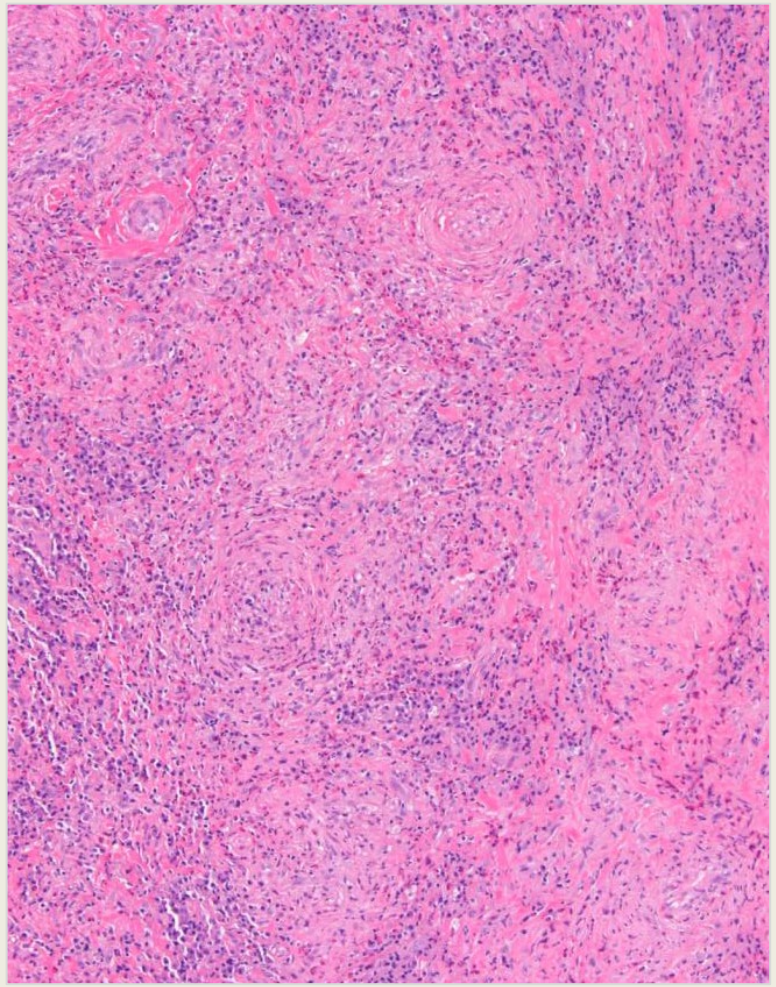
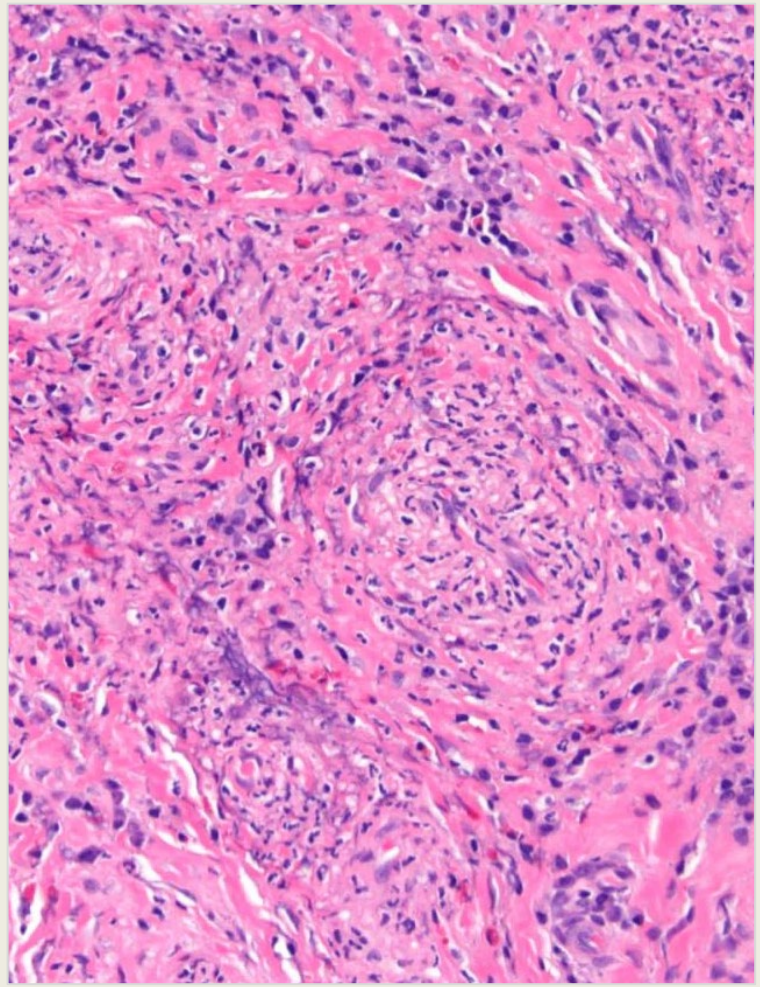
Meningeal IgG4-RD: Major Histologic Criteria



Dense lymphoplasmacytic infiltrate

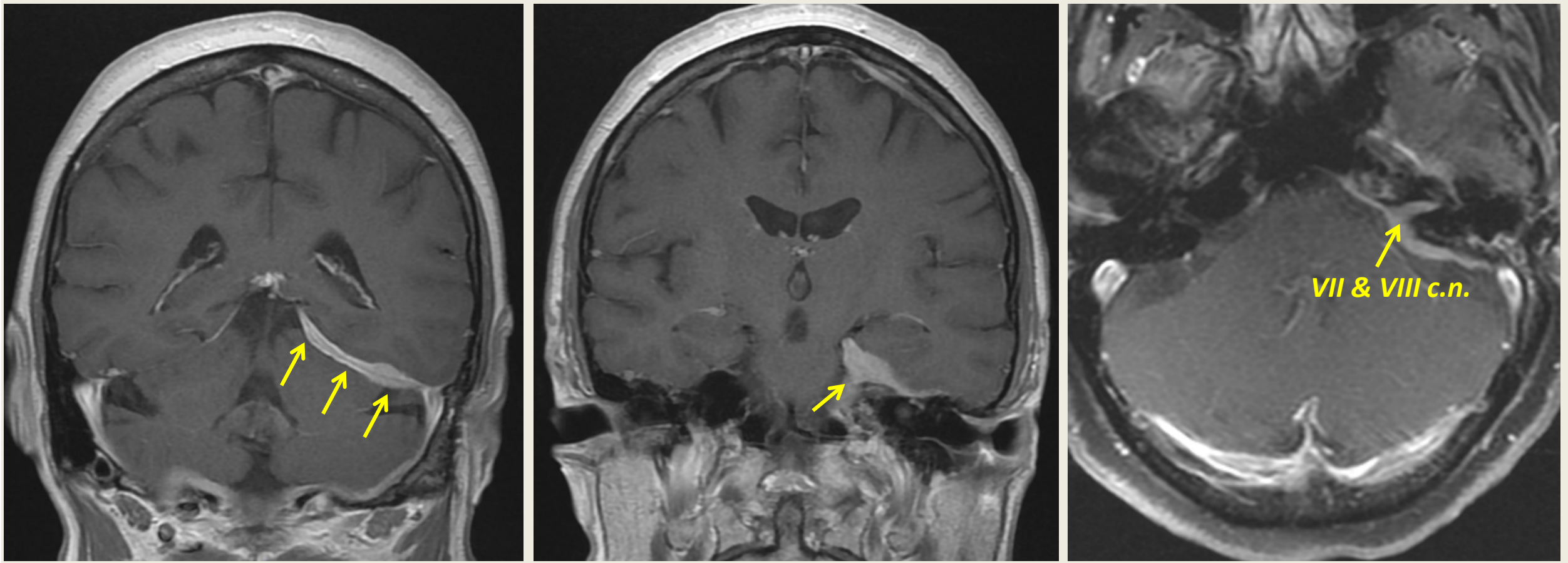


Storiform Fibrosis



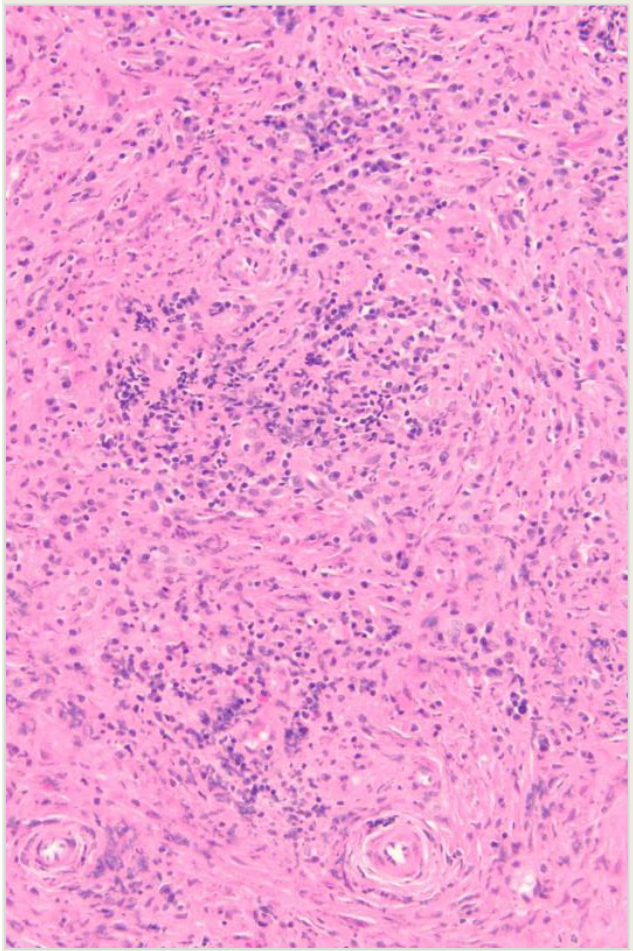
Obliterative Phlebitis

65-year-old woman with left ear and face pain

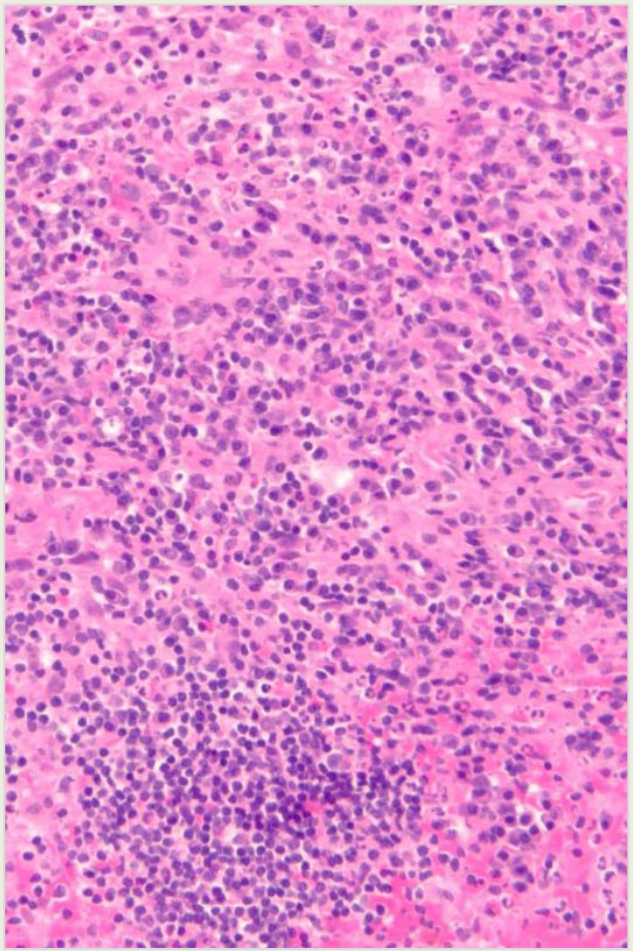


Differential diagnosis: idiopathic pachymeningitis, infectious and inflammatory granulomatous processes, granulomatosis with polyangiitis, and dural based tumors such as meningioma or less likely lymphoma and dural-based metastasis

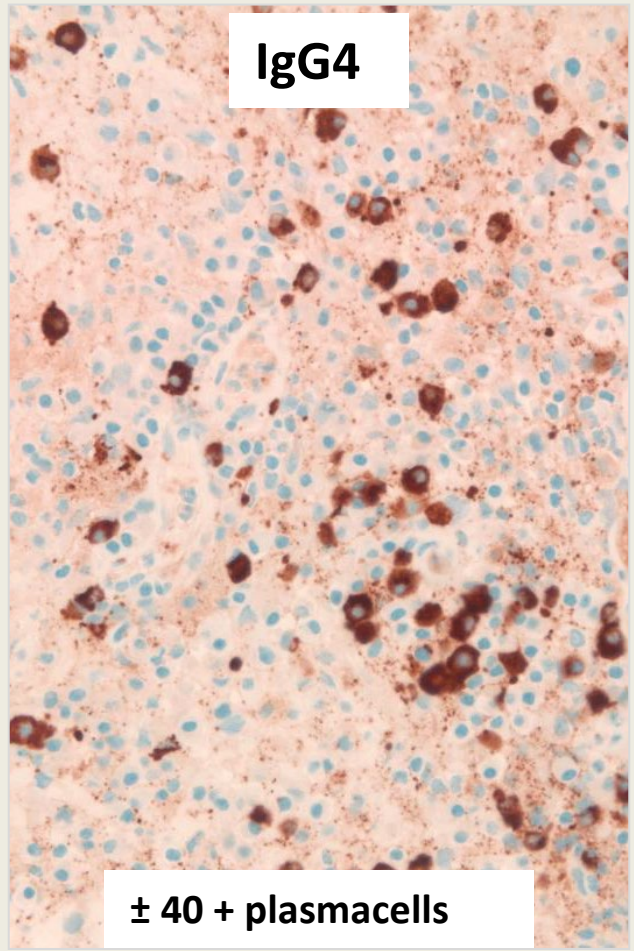
65-year-old woman with left ear and face pain

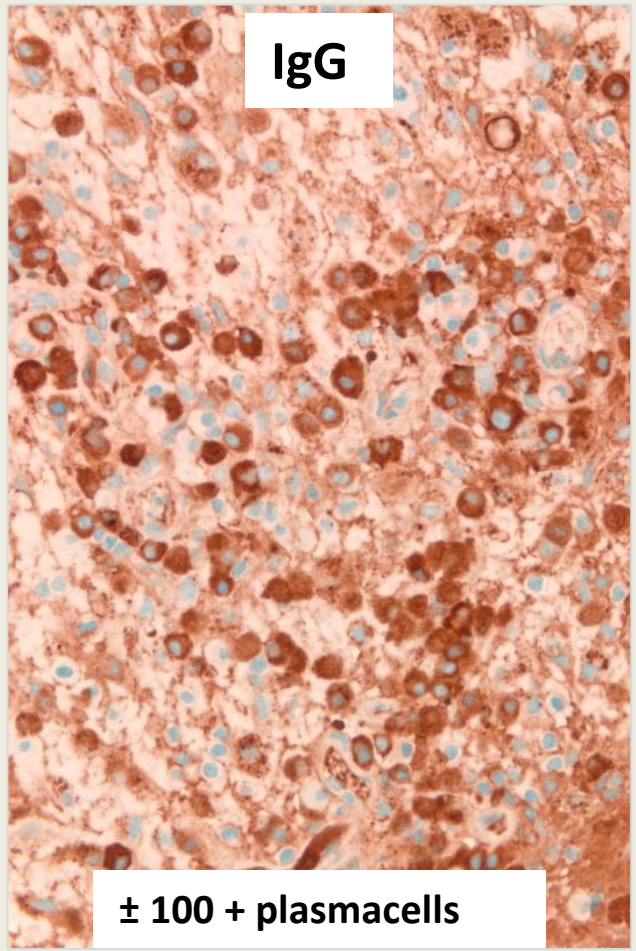


Storiform Fibrosis
at least focally



Dense lymphoplasmacytic
infiltrate





IgG4/IgG >40% (normal ratio 4-5%)

IgG4-related meningeal disease: clinico-pathological features and proposal for diagnostic criteria

#	Lymphoplasmacytic infiltration	Fibrosis	Phebitis	IgG4+ cells/HPF	IgG4/IgG ratio (%)
1	Severe; giant cells present	Minimal	Moderate	54.2	54
2	Severe	Severe	Severe	46.6	60
3	Severe	Severe	Moderate	41.6	24
4	Severe	Moderate	Minimal	11.8	30
5	Severe; lymphoid follicles; giant cells present	Severe	Moderate	26.8	–
6	Moderate	None	None	0.4	1
7	Minimal	Severe	None	0	0
8	Minimal	Severe	None	0	0
9	Moderate; lymphoid follicles	Moderate	None	2.2	8
10	Moderate	None	None	0.2	1

IgG4-related meningeal disease: clinico-pathological features and proposal for diagnostic criteria

Comparison of IgG4-related and non-IgG4-related cases

	IgG4-related (n = 5)	Non-IgG4-related (n = 5)	P
IgG *	97.3 (39.8–71.4)	17.6 (0–40.2)	0.001
IgG4*	36.2 (11.8–54.2)	0.6 (0–2.2)	0.02
IgG4/IgG ratio (%)	42 (24–60)	3 (0–8)	0.01

* Positive plasma cells / HPF

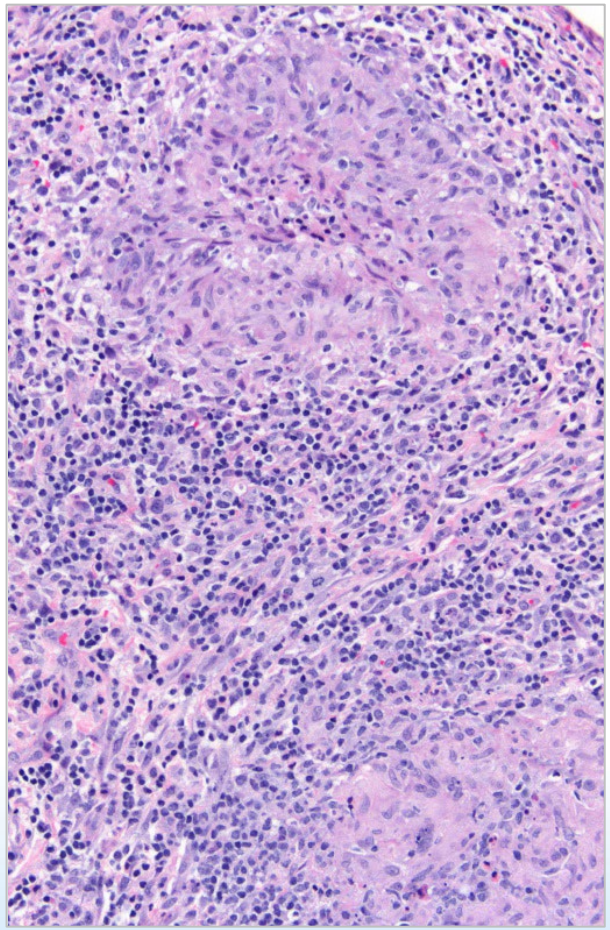
Acta Neuropathol 2010;120:765-76

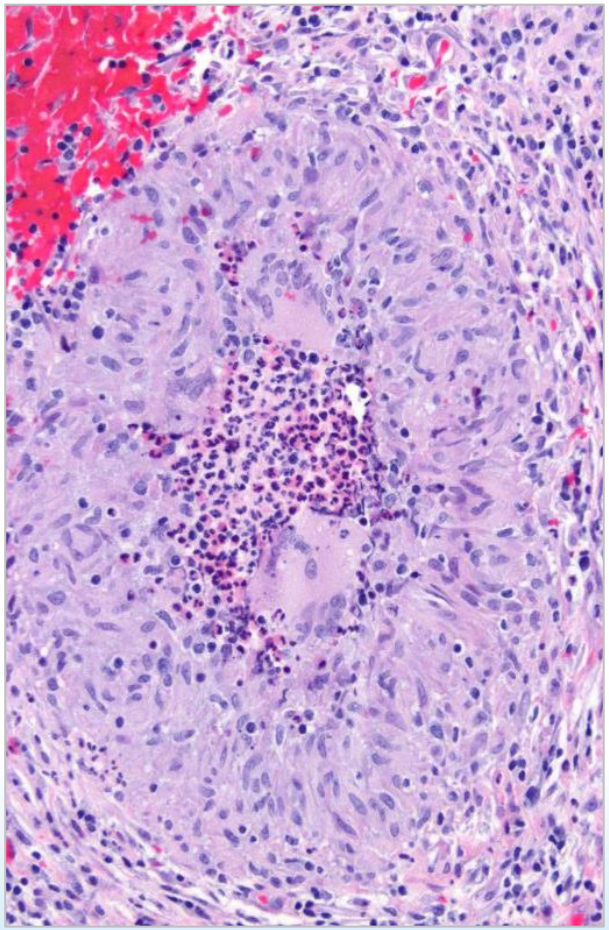
Meningeal IgG4-Related Disease: Diagnostic Histologic Criteria

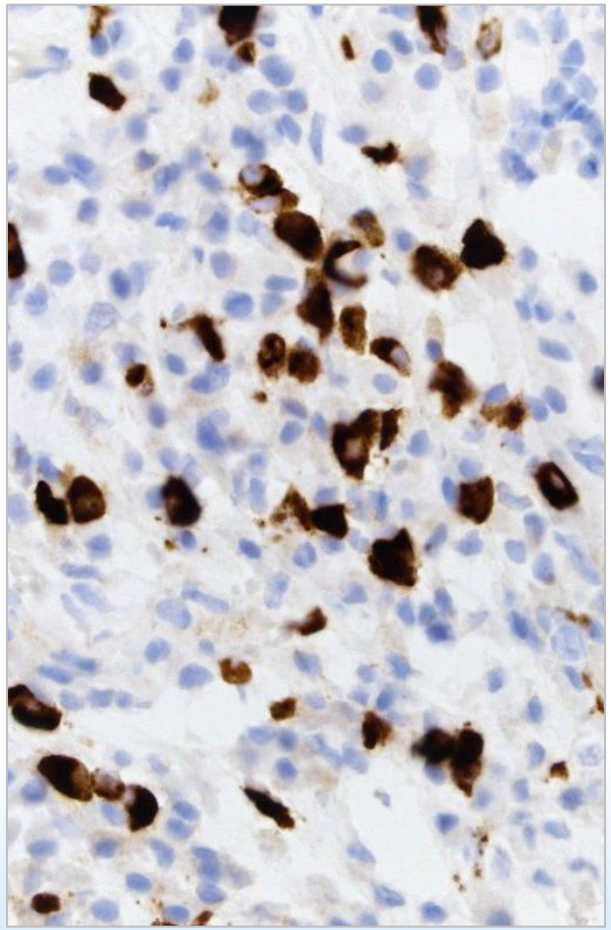
- The major histologic features associated with IgG4 related disease include:
  - Dense lymphoplasmacytic infiltrate
  - Fibrosis, arranged at least focally in a storiform pattern
  - Obliterative phlebitis
- Additional features include:
  - Phlebitis without obliteration of the lumen
  - Increased numbers of eosinophils
- Features **inconsistent** with IgG4 related disease include:
  - Epithelioid cell granulomas and prominent neutrophilic infiltrate

Mod Pathol. 2012 Sep;25(9):1181-92

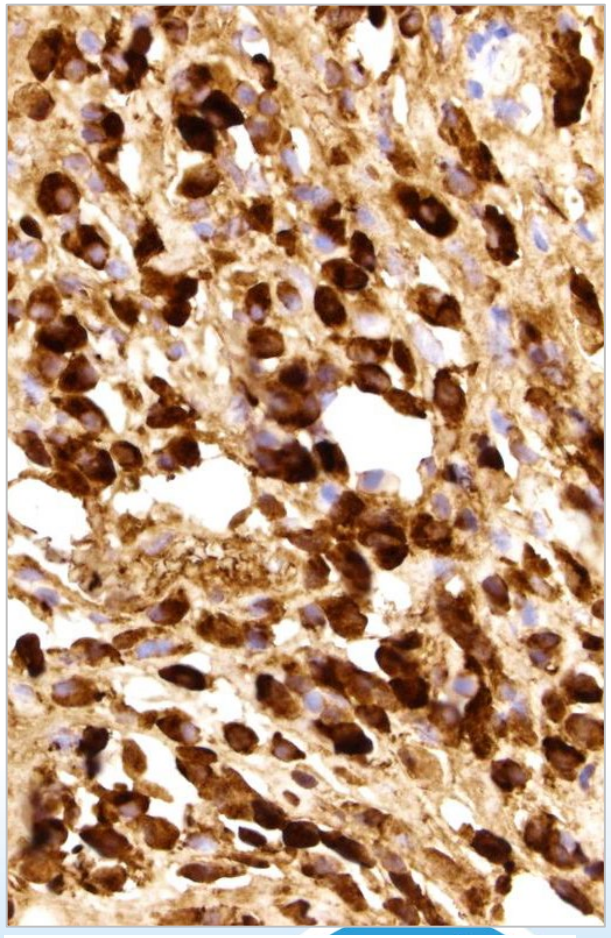
Two Features **Inconsistent** with IgG4 Related Disease
Epithelioid Cell granulomas and Prominent Neutrophilic Infiltrate







IgG4 (>30/HPH)

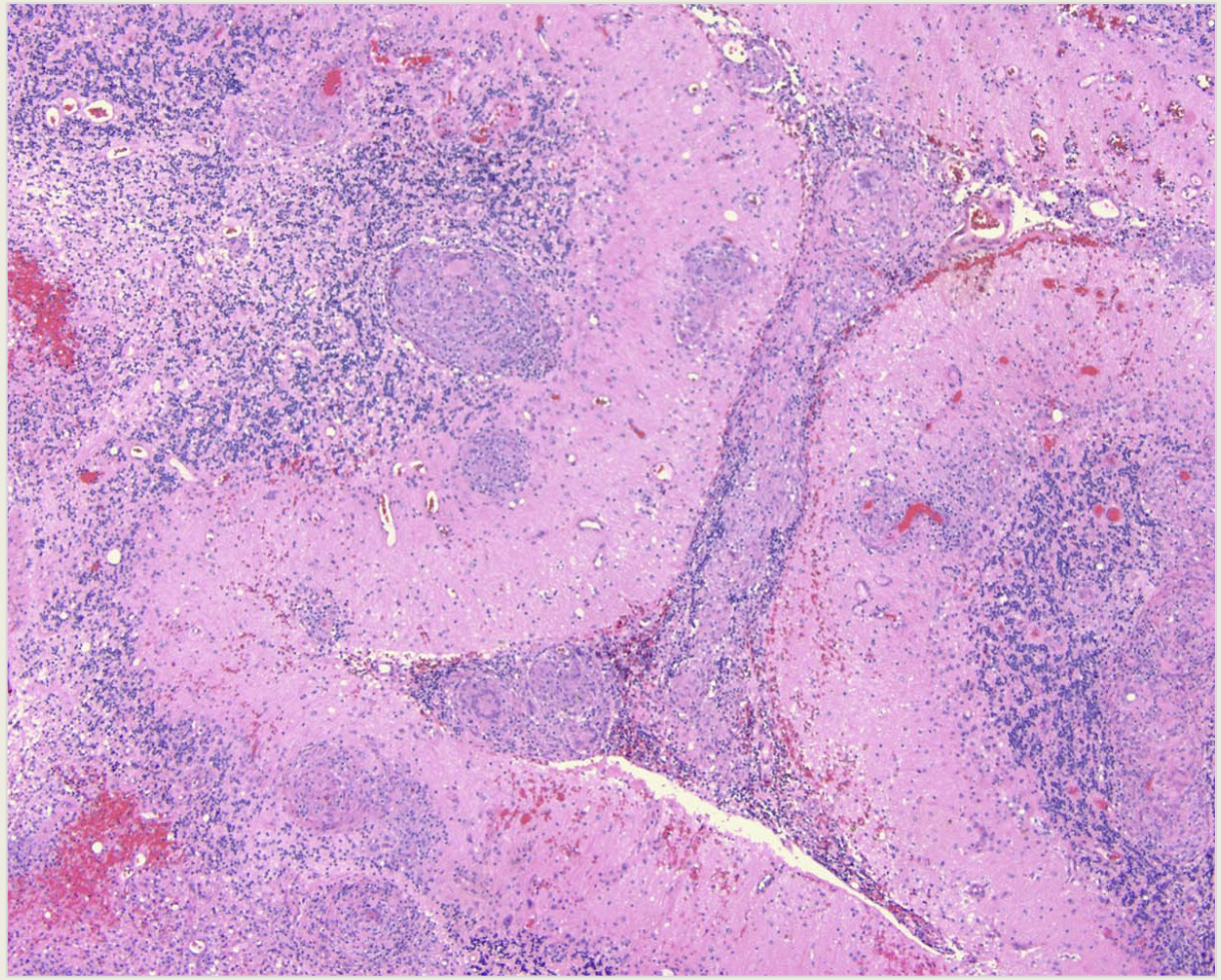


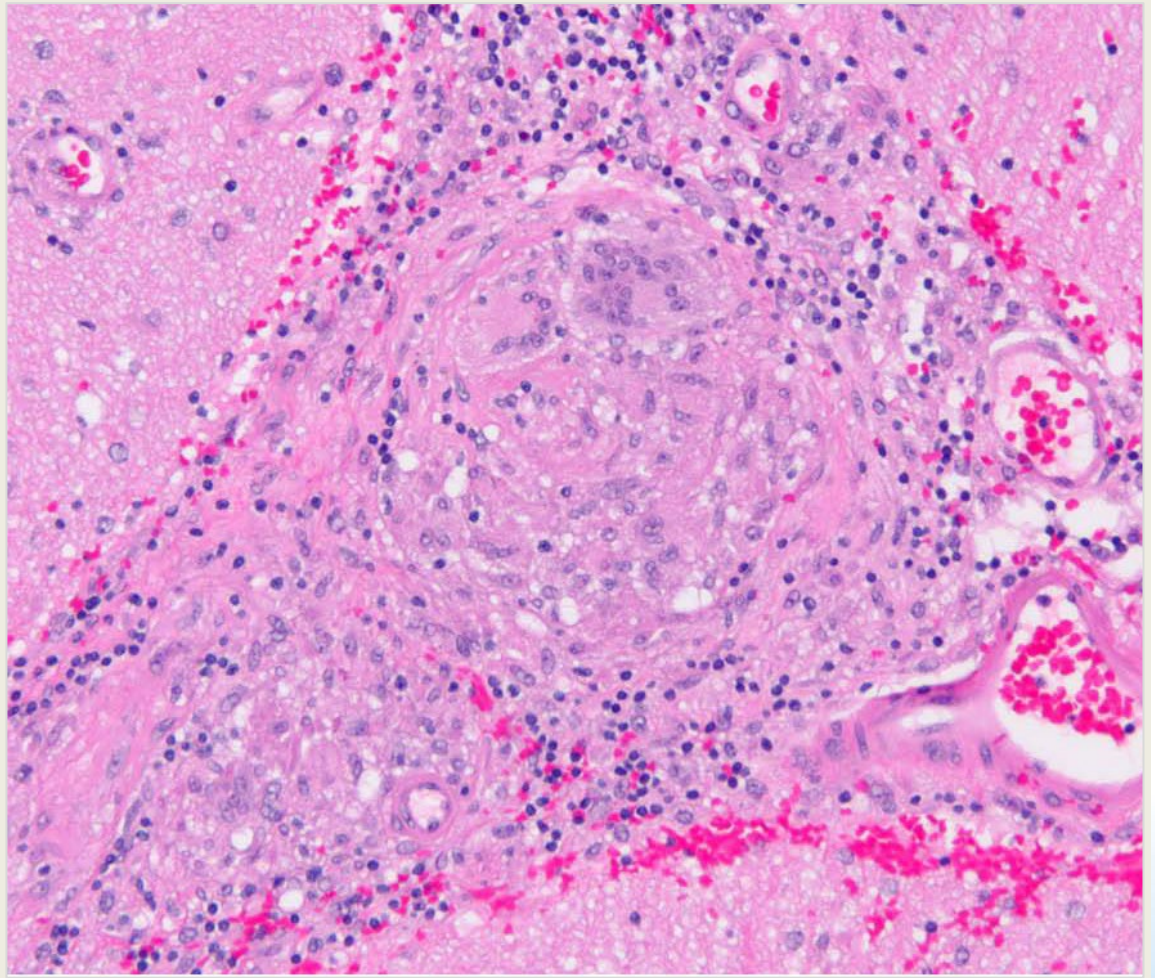
IgG (IgG/IgG4 ratio ± 30%)

Sarcoidosis and The Nervous System

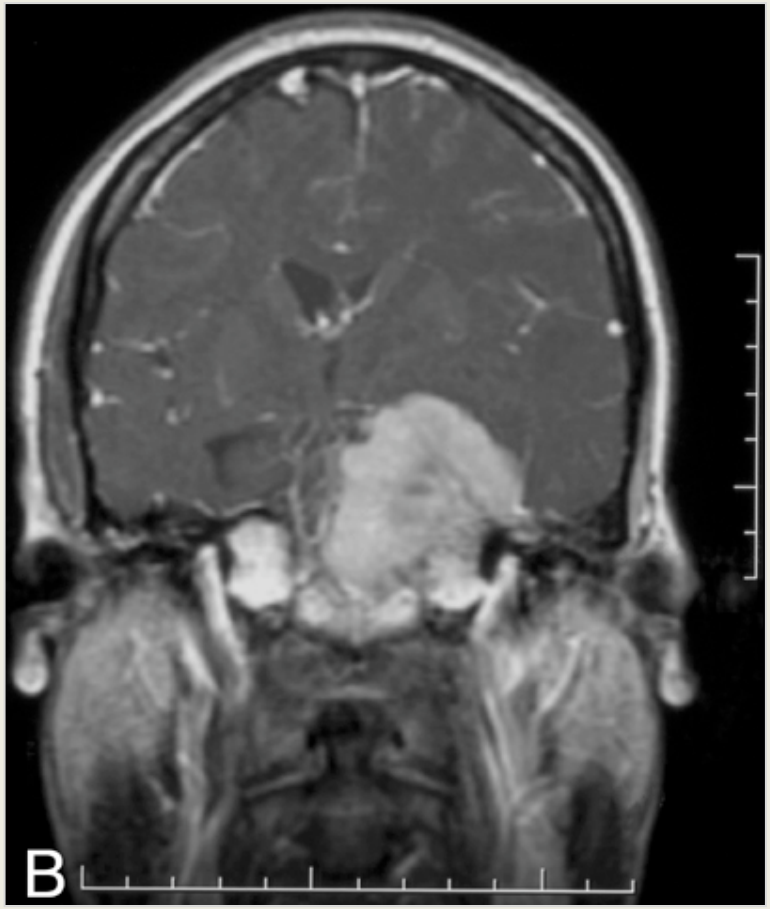
- Worldwide disease – regional ethnic predilection (african american in USA, white people in Europe/Sweden)
- Non necrotizing granulomatous inflammation
  - Well formed granulomas
  - Presence of giant cells
- Central Nervous System (Brain and Spinal cord)
  - Intraparenchymal lesions
  - Leptomeningeal involvement
  - Dura based mass mimicking meningioma
- Peripheral Nervous System

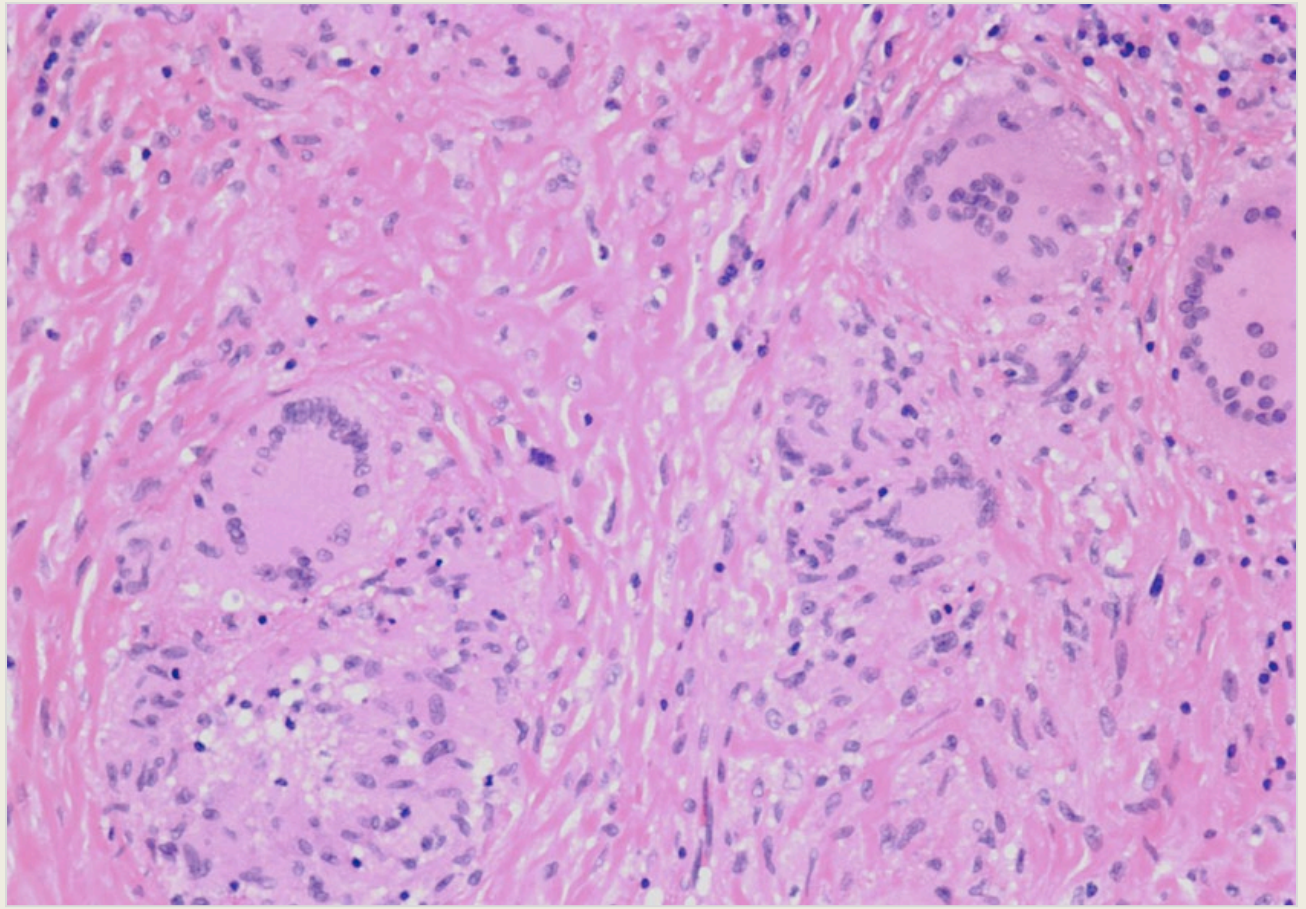
Leptomeningeal & Parenchymal Granulomatous Inflammation





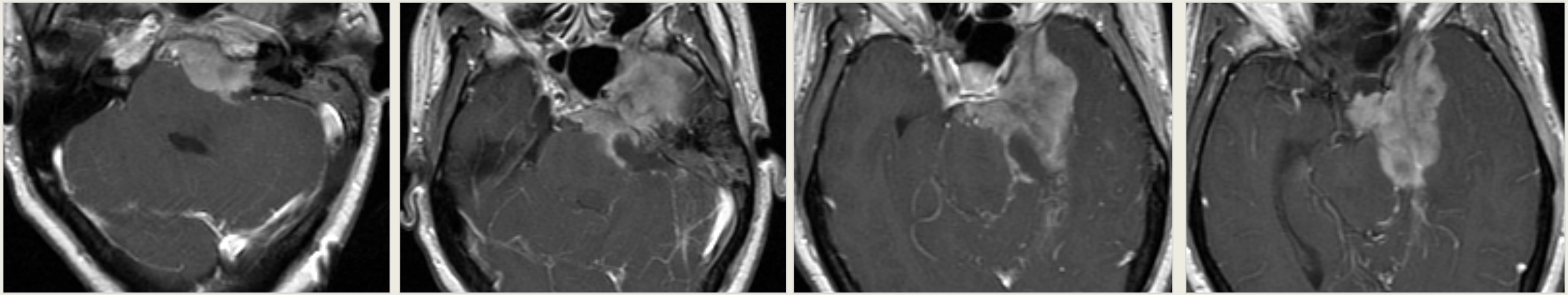
Sarcoidosis mimicking Meningioma



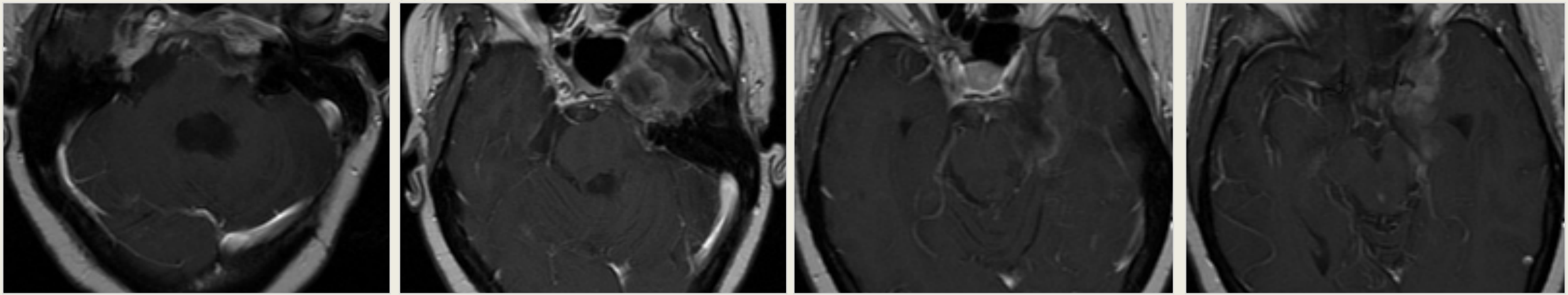


Sarcoidosis mimicking Meningioma

Immediately Postoperatively



Following Steroid Therapy for approximately a year

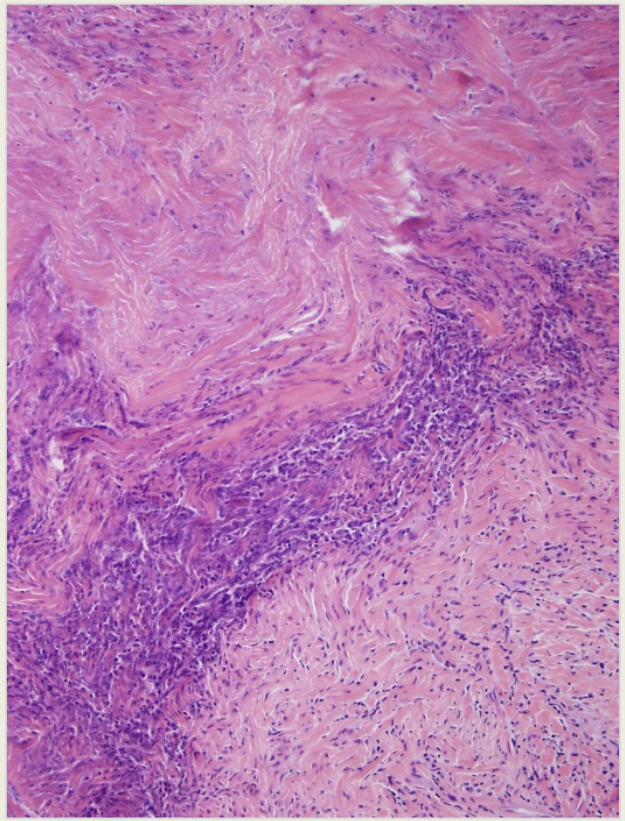


Granulomatosis with Polyangiitis: Current Definition

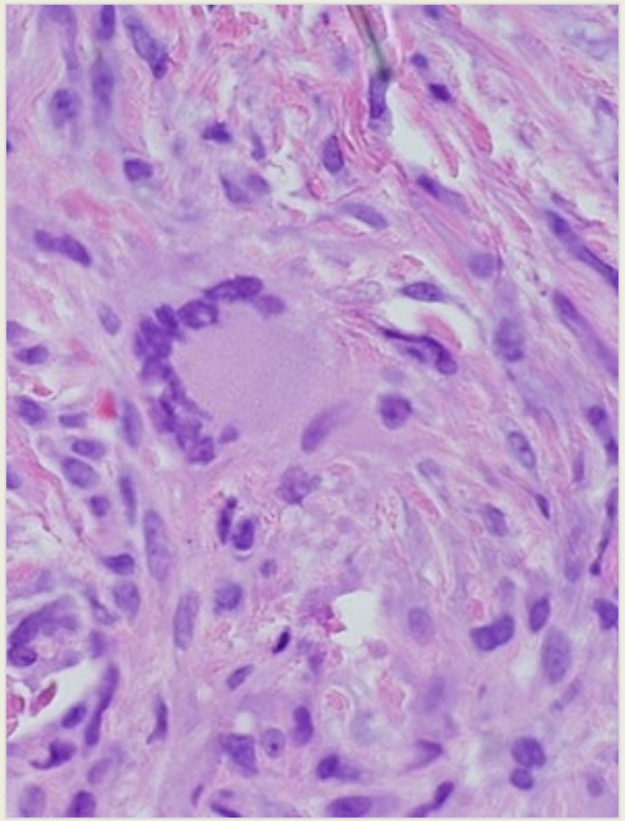
- Form of systemic vasculitis
- Any organ may be involved
  - Upper respiratory tract, lung or kidney – involvement of all 3 sites uncommon
  - CNS involvement, especially in isolation, is rare
- Microscopically associated with necrotizing “granulomatous” lesions
- ANCA (usually cANCA) positive
  - Stimulus initiating the autoantibody (ANCA) formation is not yet known
  - ANCA activates neutrophils
  - Neutrophils release cytokines with damage of endothelial cells
  - Cellular interactions - inflammation

Granulomatosis with Polyangiitis: Classic “full blown” Lesions

Geographic Necrosis

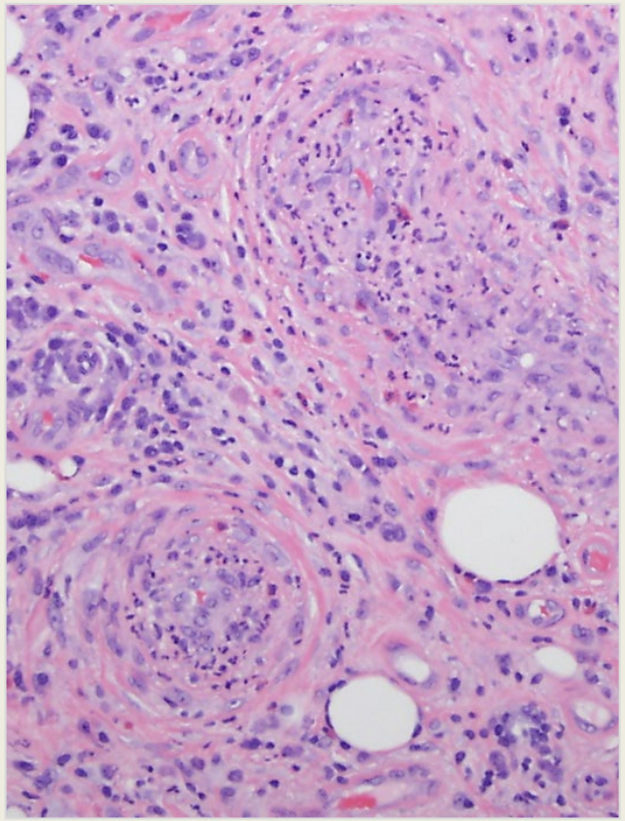


Granulomatous Inflammation

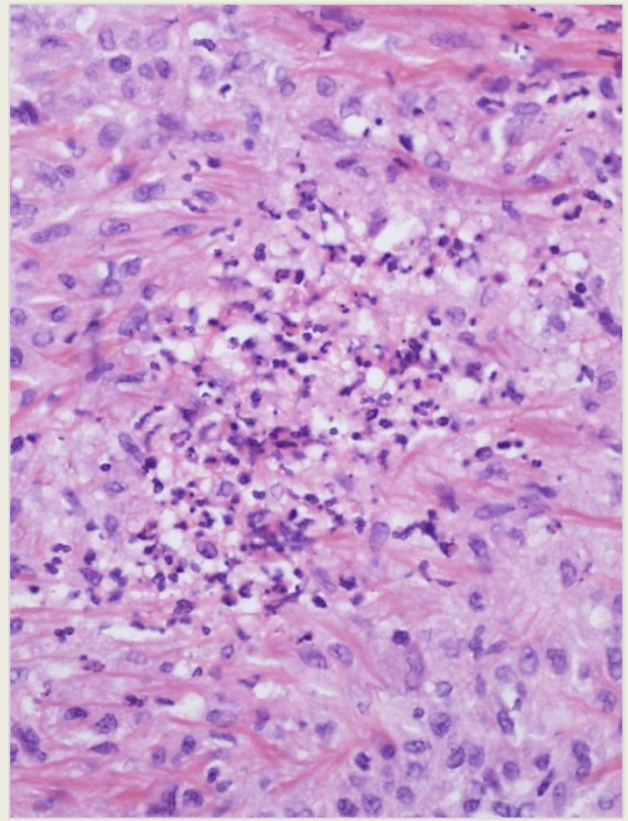


Surrounding areas of necrosis

Small Vessel Vasculitis

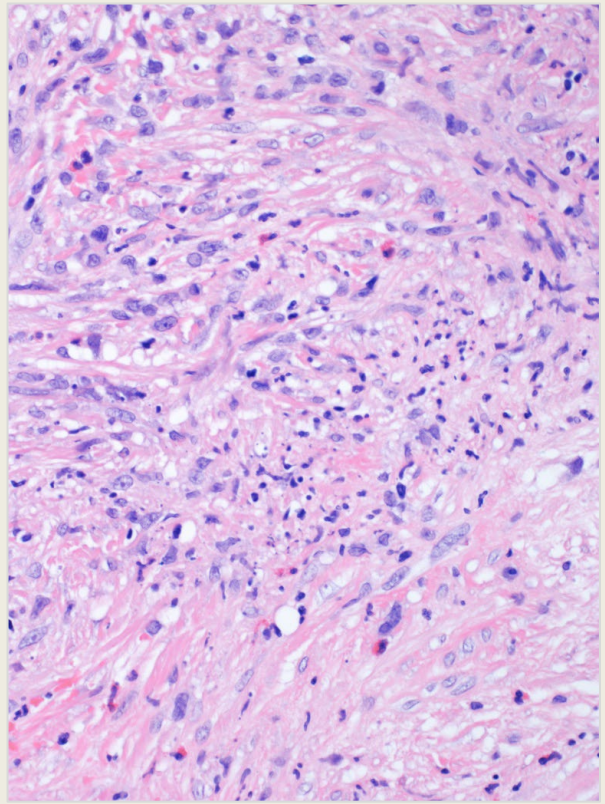


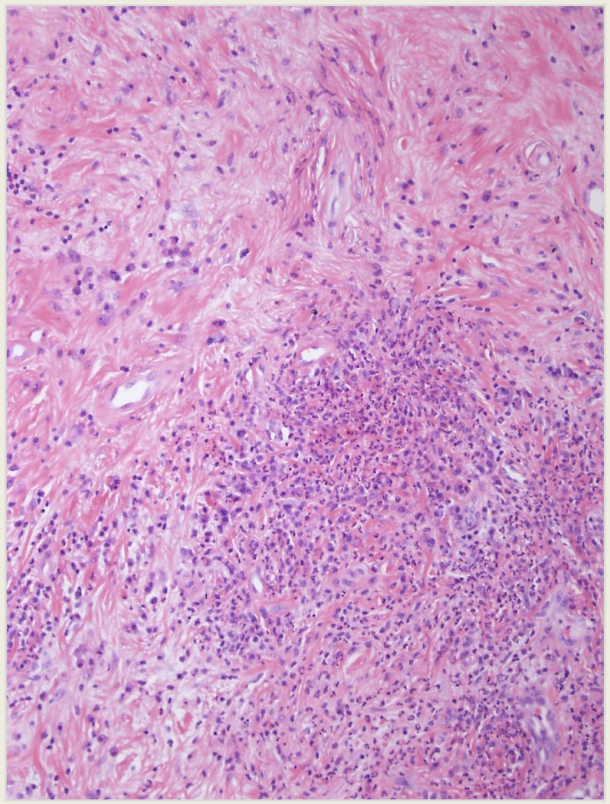
Inflammatory Background



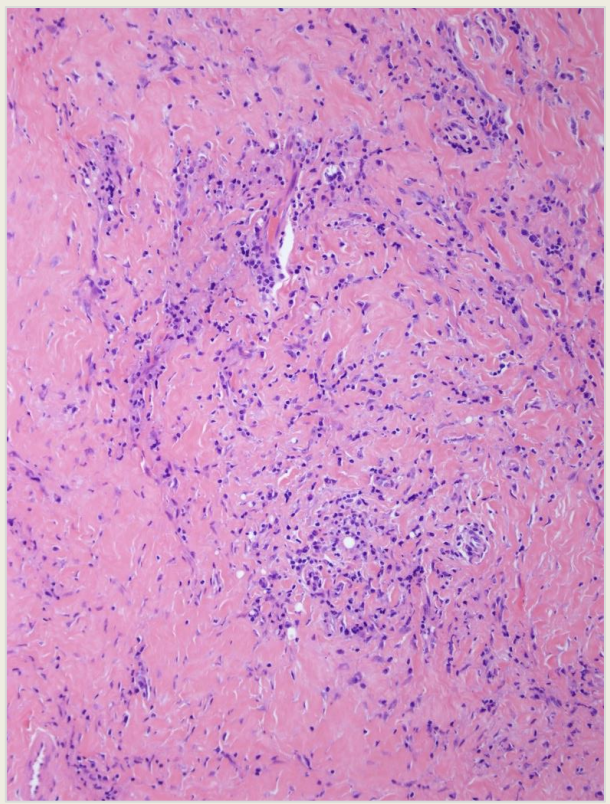
Neutrophils

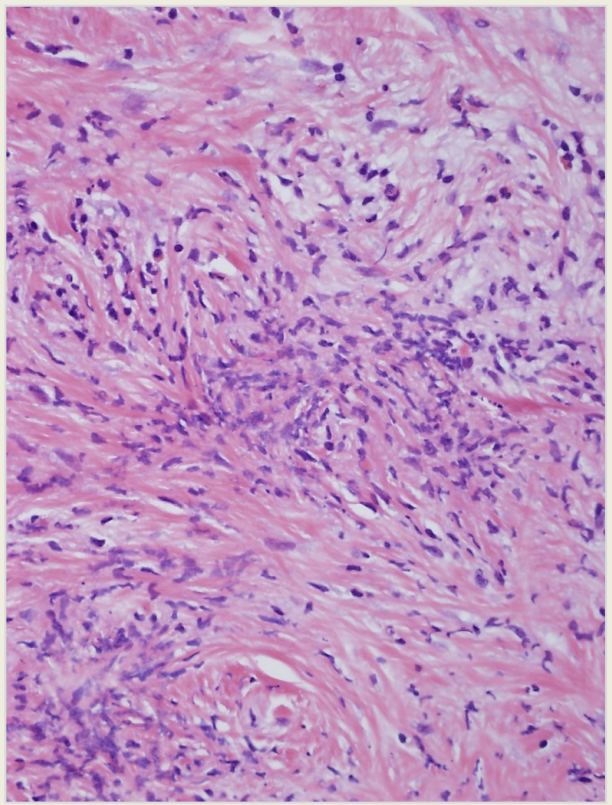
Granulomatosis with Polyangiitis: Early Lesions





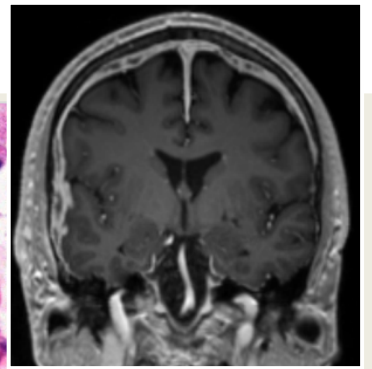
Microscopic Collections of Neutrophils - Microabscess

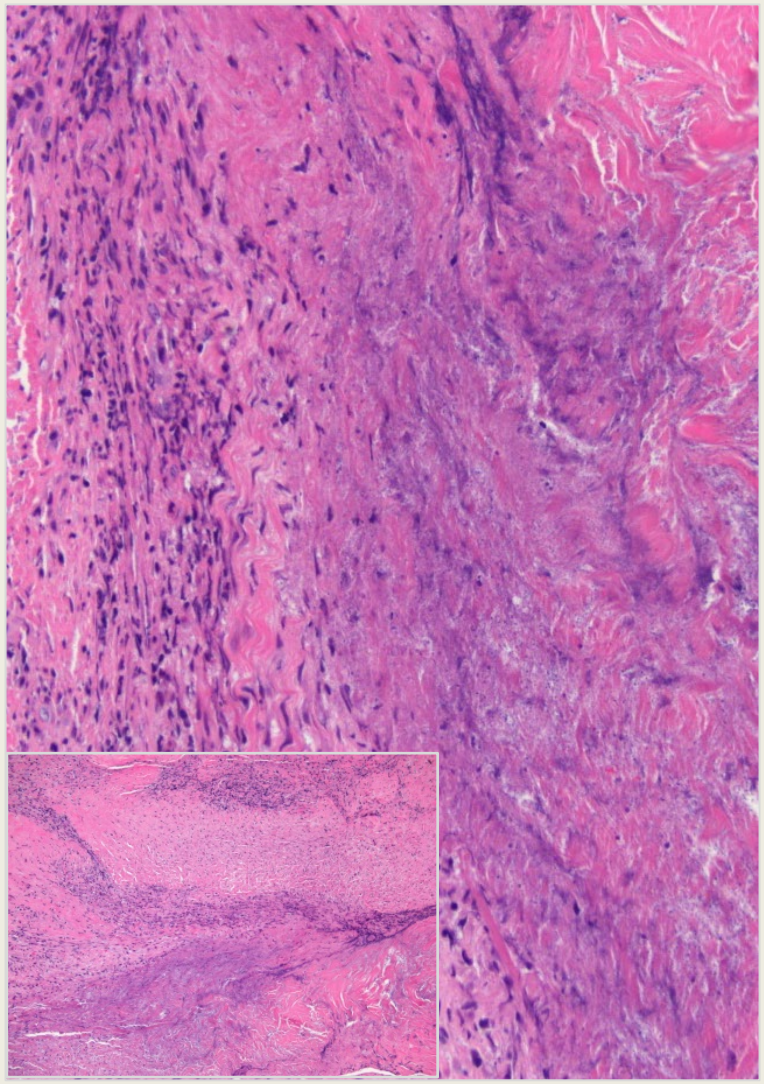


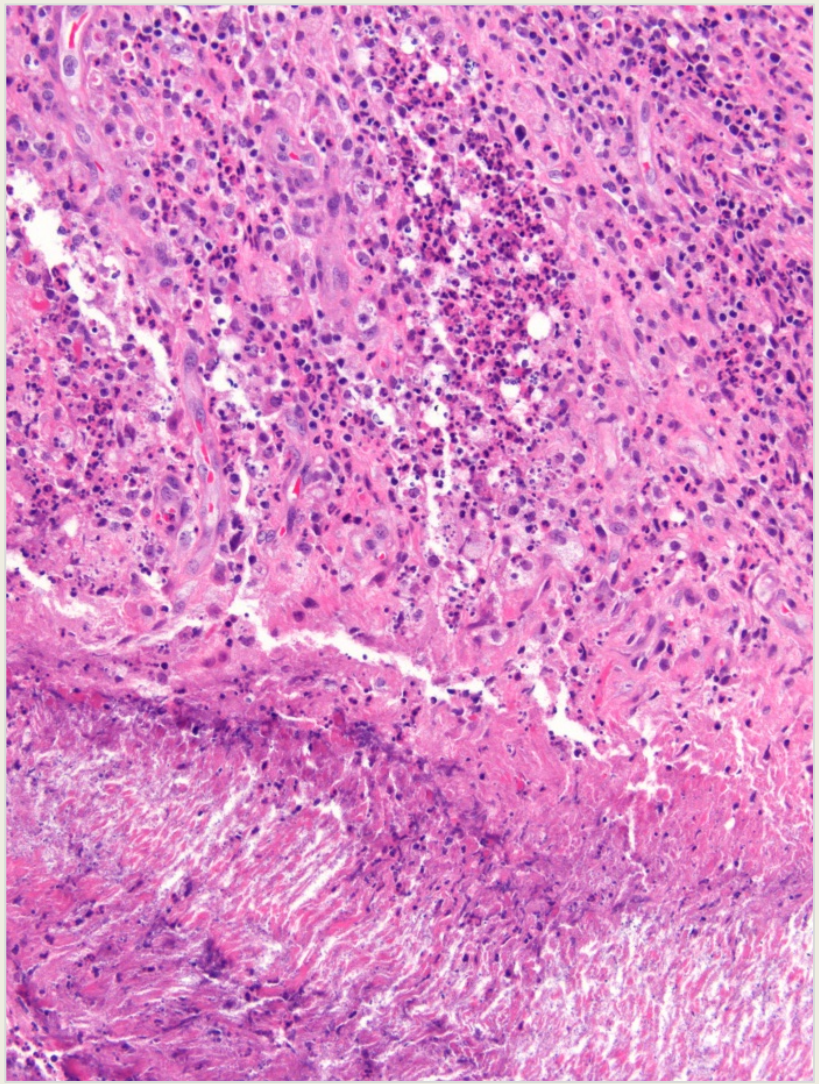


Neutrophilic Necrosis & Collagen Necrosis

66-year-old M - bilateral pachymeningeal thickening







Rheumatoid Arthritis

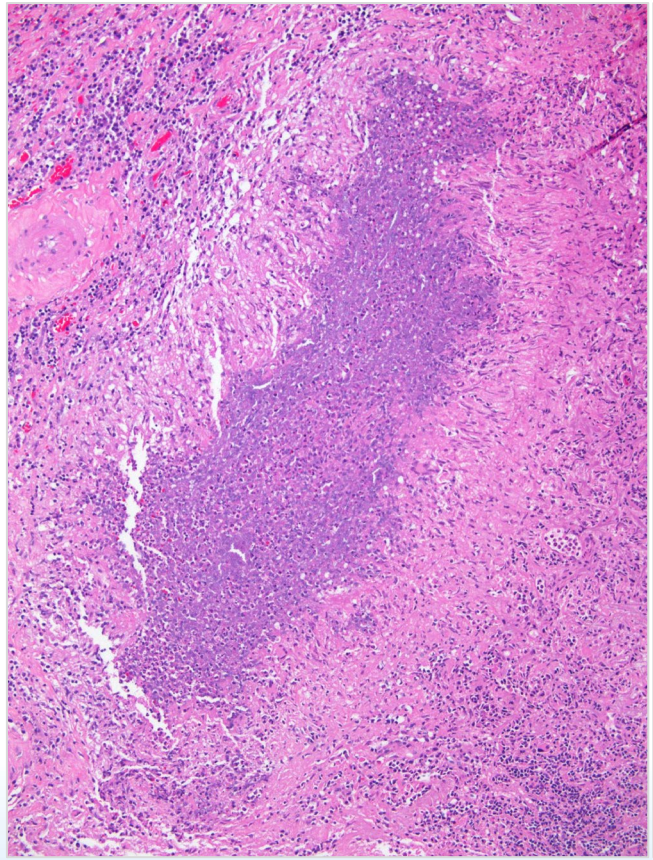
- Chronic inflammatory disorder with symmetric, peripheral erosive polyarthritis of unknown etiology
- Extra-articular manifestations: lungs, kidneys, heart, skin, eyes, muscle, peripheral and central nervous systems
- CNS & PNS involvement & manifestations in RA
  - Extradural pannus or vertebral body collapse with spinal cord compression (atlanto-axial subluxation)
  - Peripheral neuropathy
  - Meningitis

Rheumatoid Meningitis

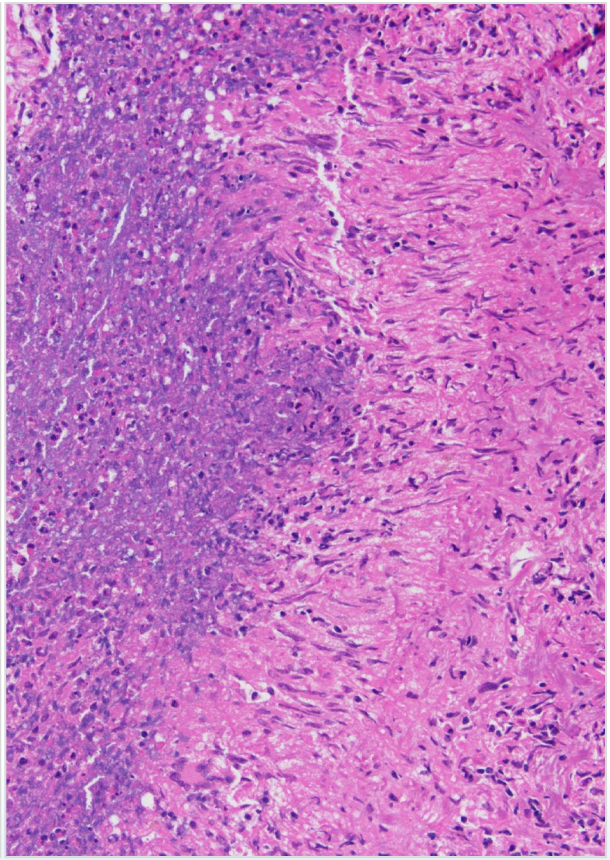
- Rare, most commonly occurs in the setting of longstanding severe RA
  - In a review of 48 cases, 50% of patients had a history of RA for 10 or more years
  - Only in 5 patients, there was no prior RA history, but developed joint symptoms at the time or shortly after onset of meningitis
- Pachymeningitis and/or leptomeningitis
  - Meningeal inflammation (83%), rheumatoid nodules (56%), vasculitis (38%)
- Focal neurologic symptoms / cranial neuropathy most frequent
  - Also cognitive dysfunction, seizures, headaches
- In the past (before 1985) high mortality, often diagnosed at autopsy

Neuropathology 2016; 36, 93–102

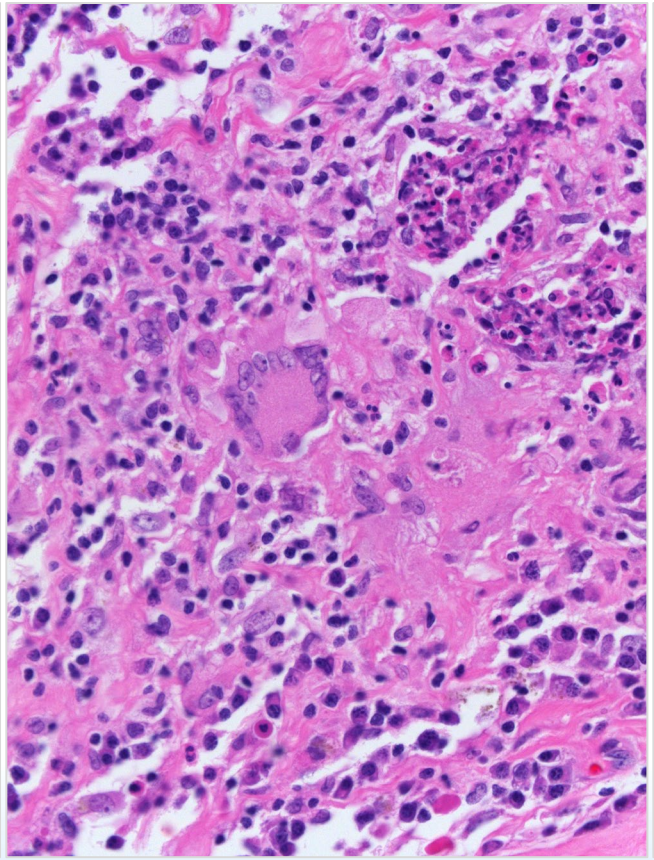
69 F – known history of rheumatoid arthritis
MRI coarse confluent leptomeningeal enhancement



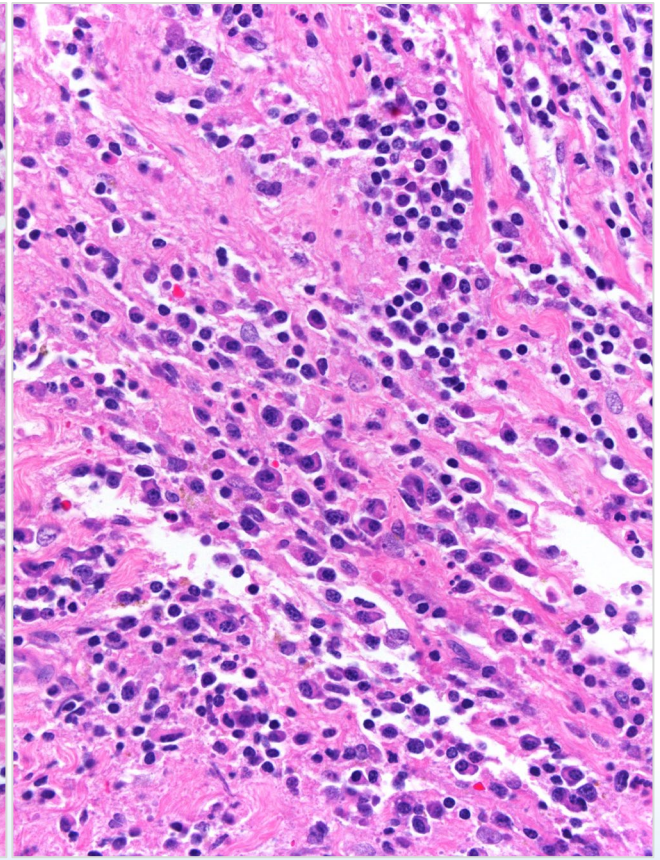
Rheumatoid nodule



Surrounding epithelioid histiocytes

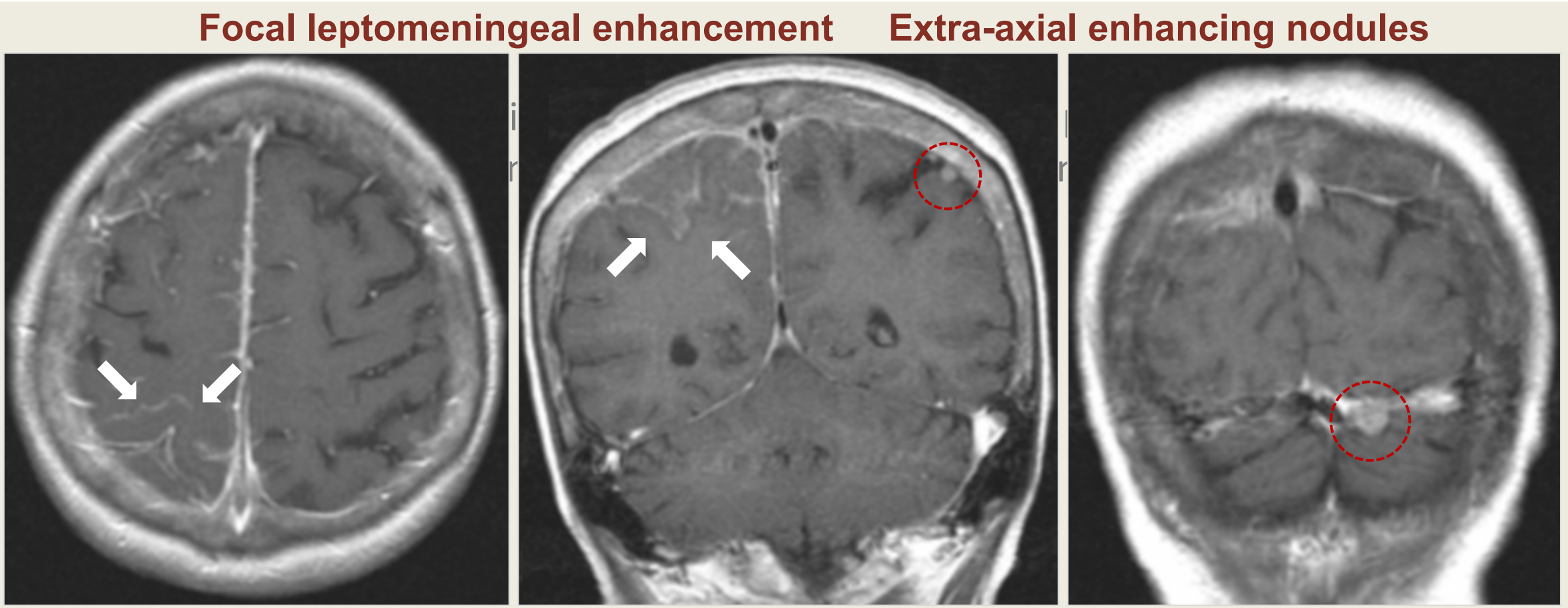


Giant cells

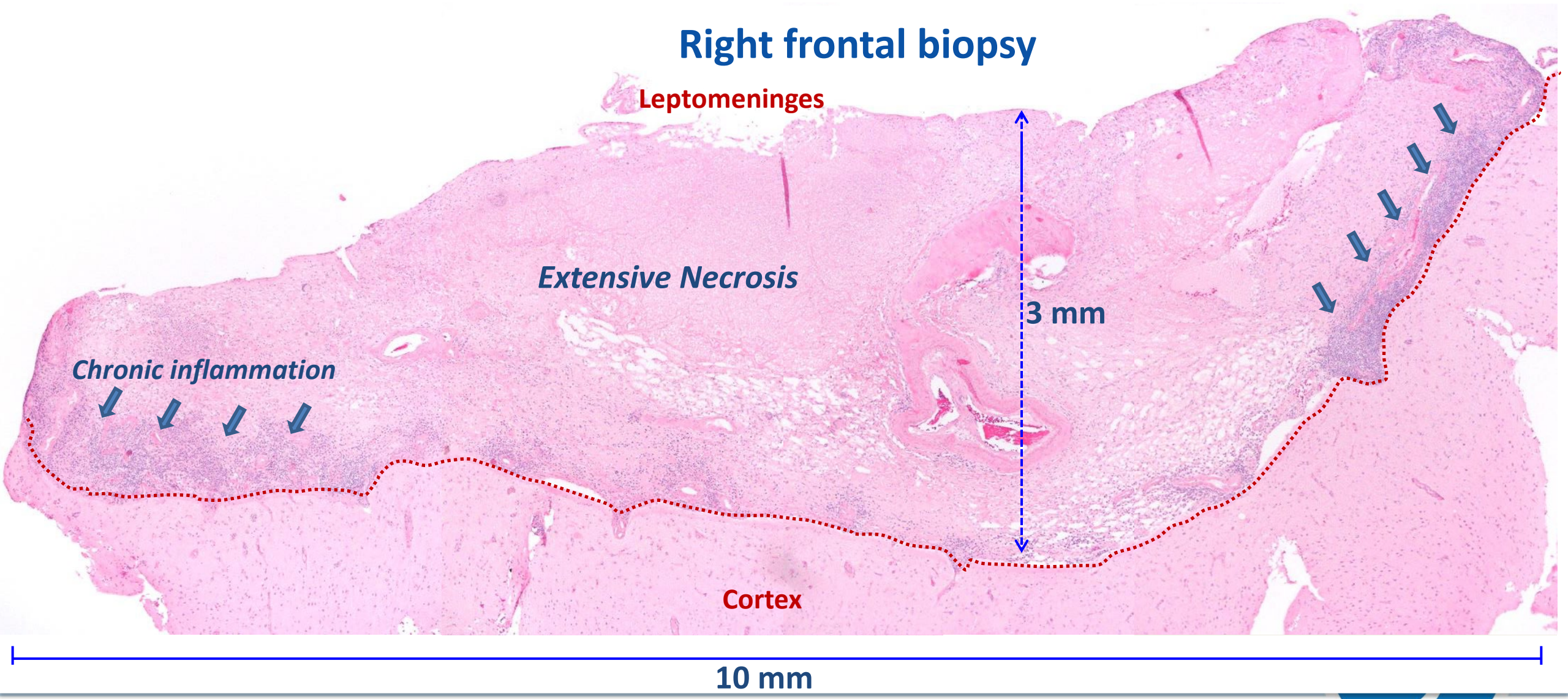


Plasma cell predominance

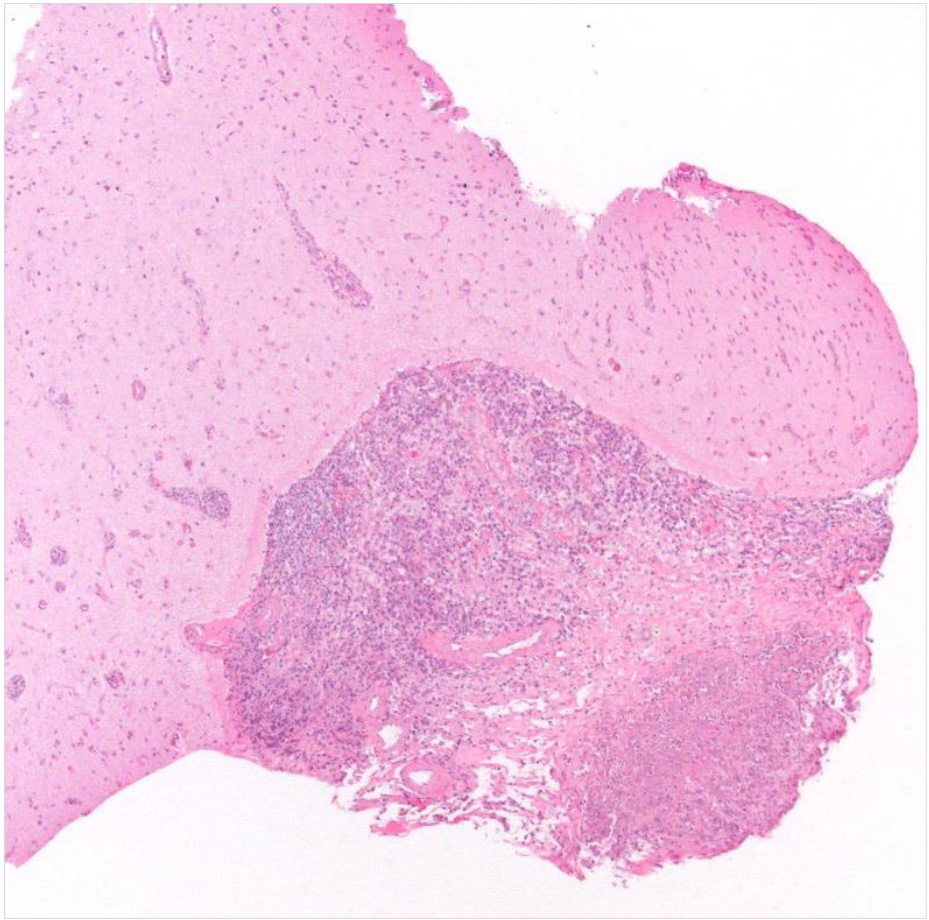
78-year-old, Rheumatoid Arthritis (10 years)

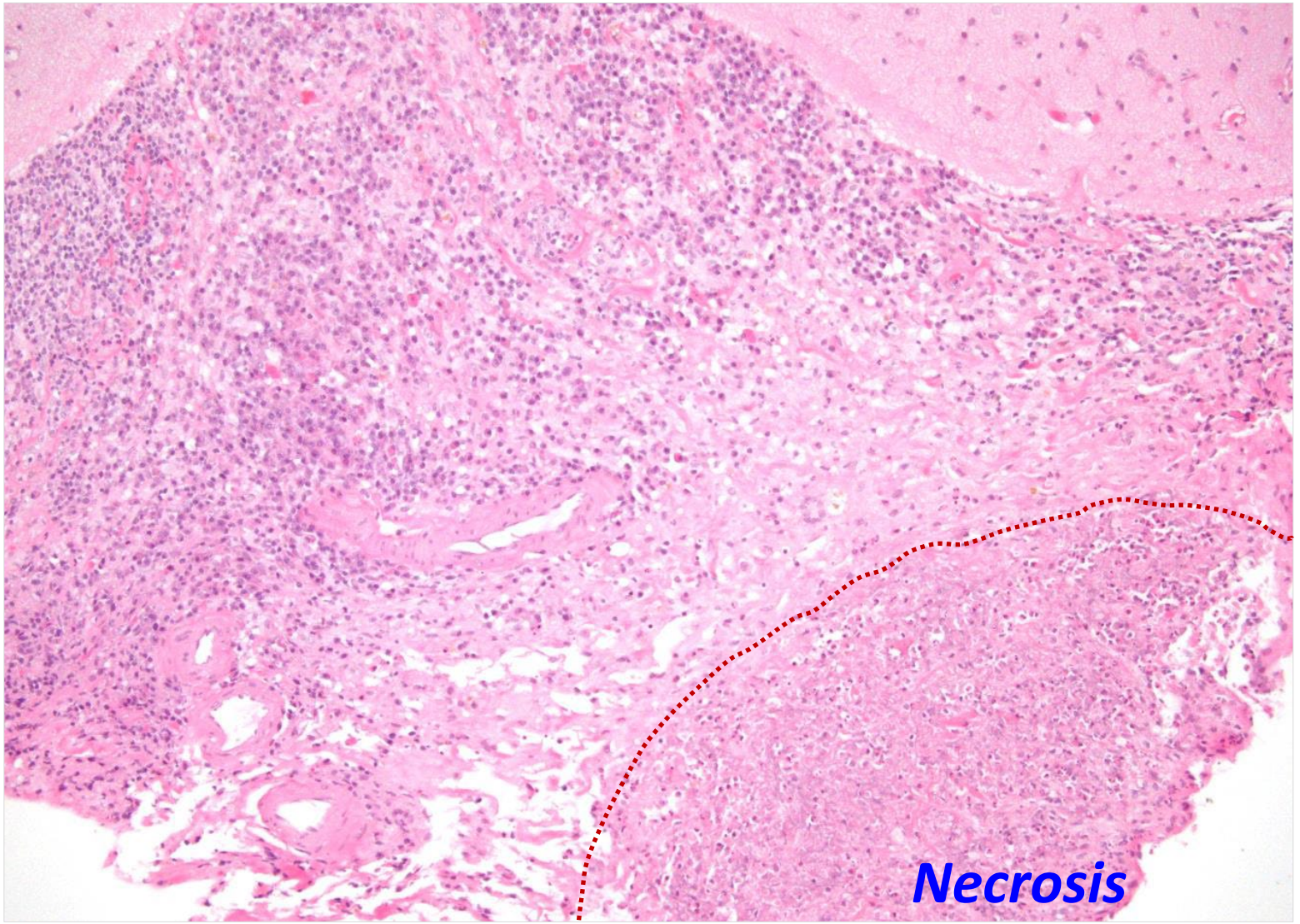


Rheumatoid Meningitis

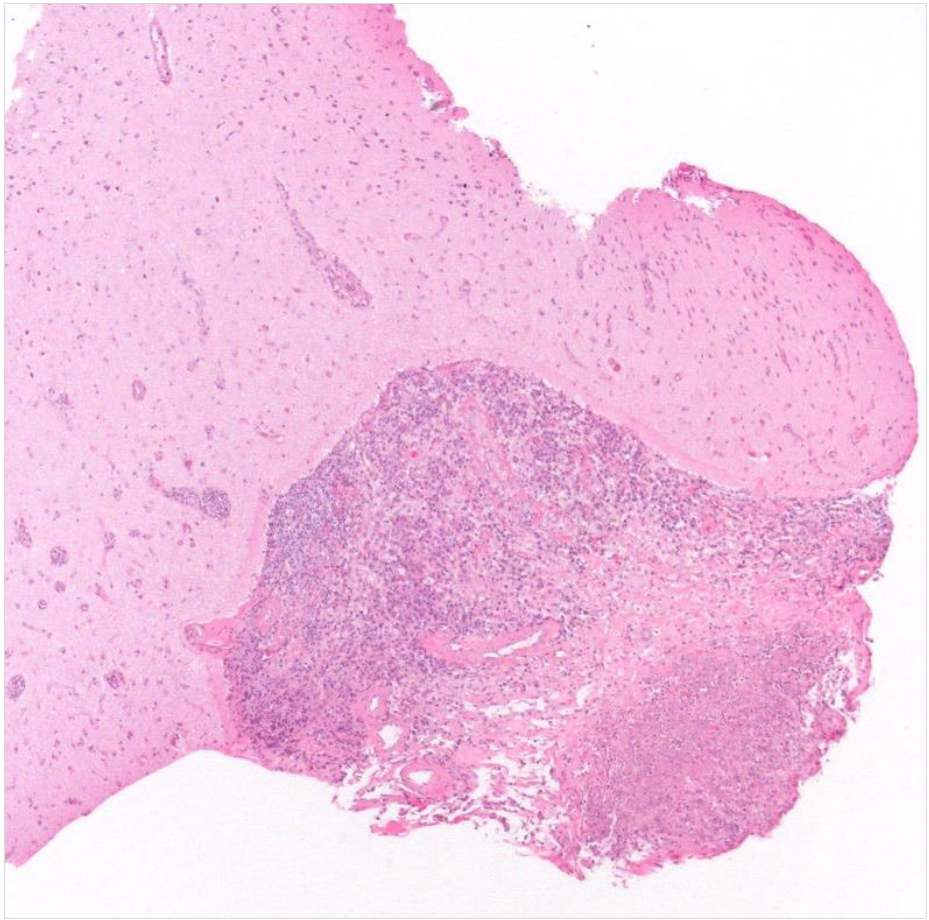


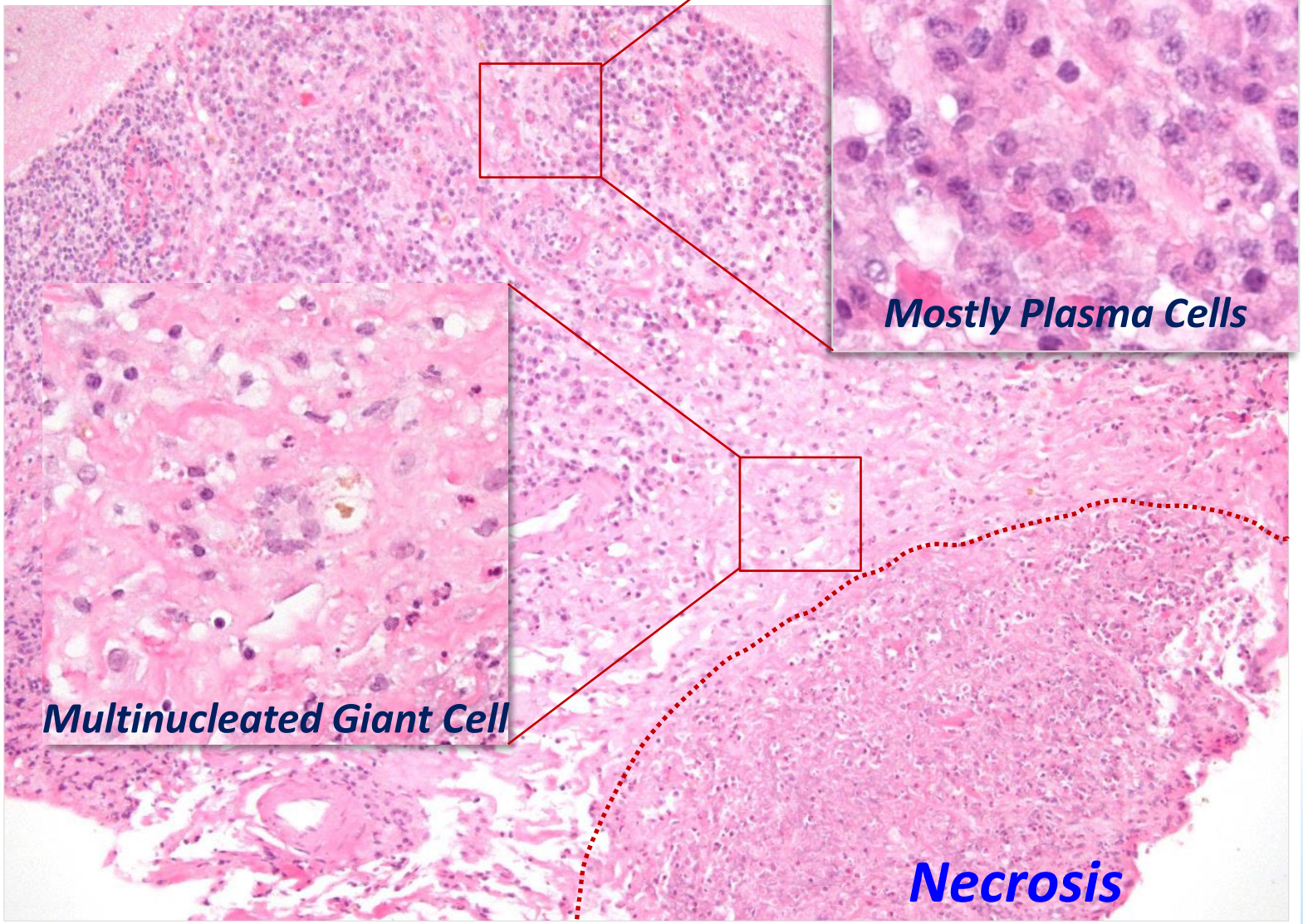
Rheumatoid Meningitis





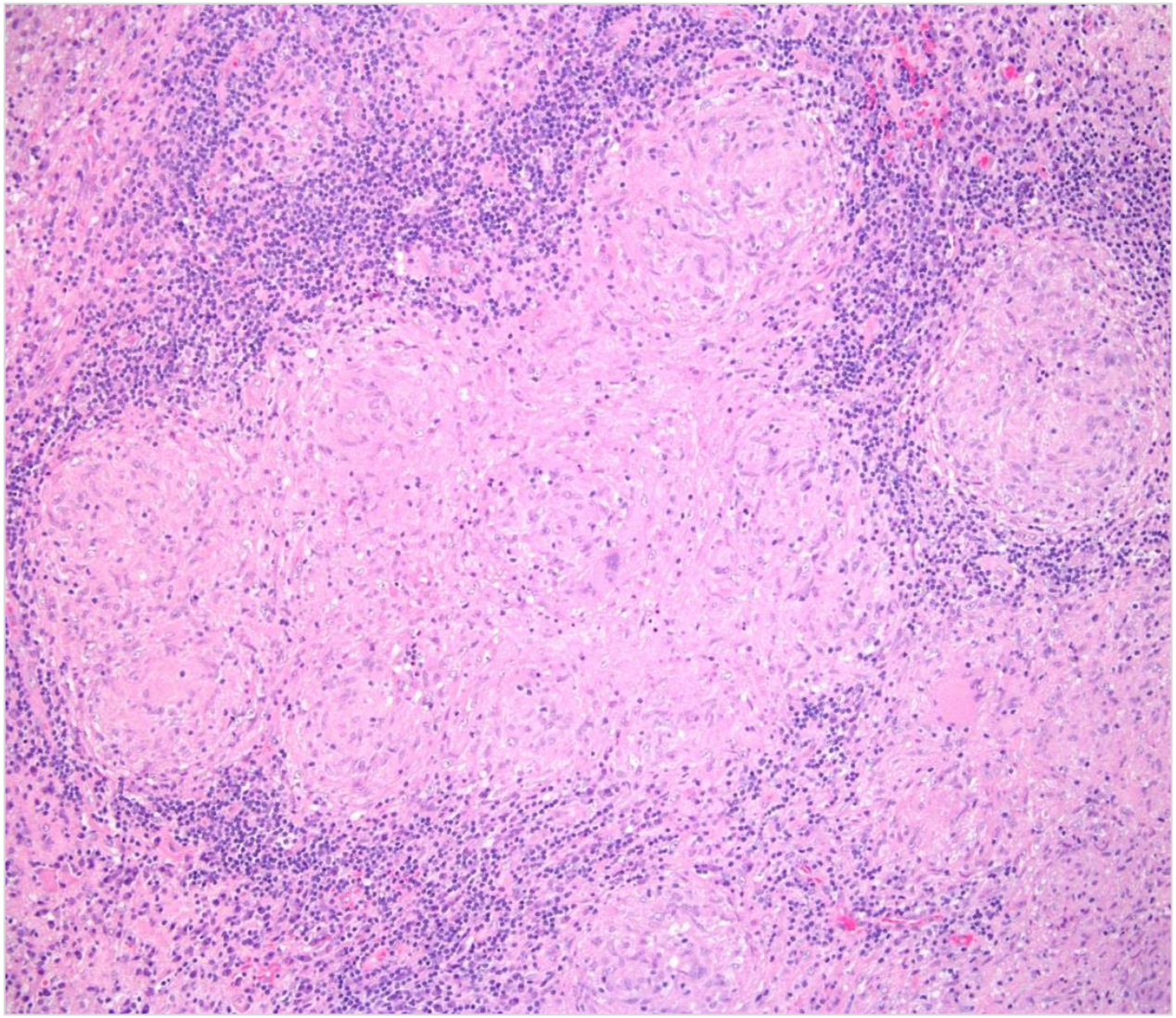
Rheumatoid Meningitis

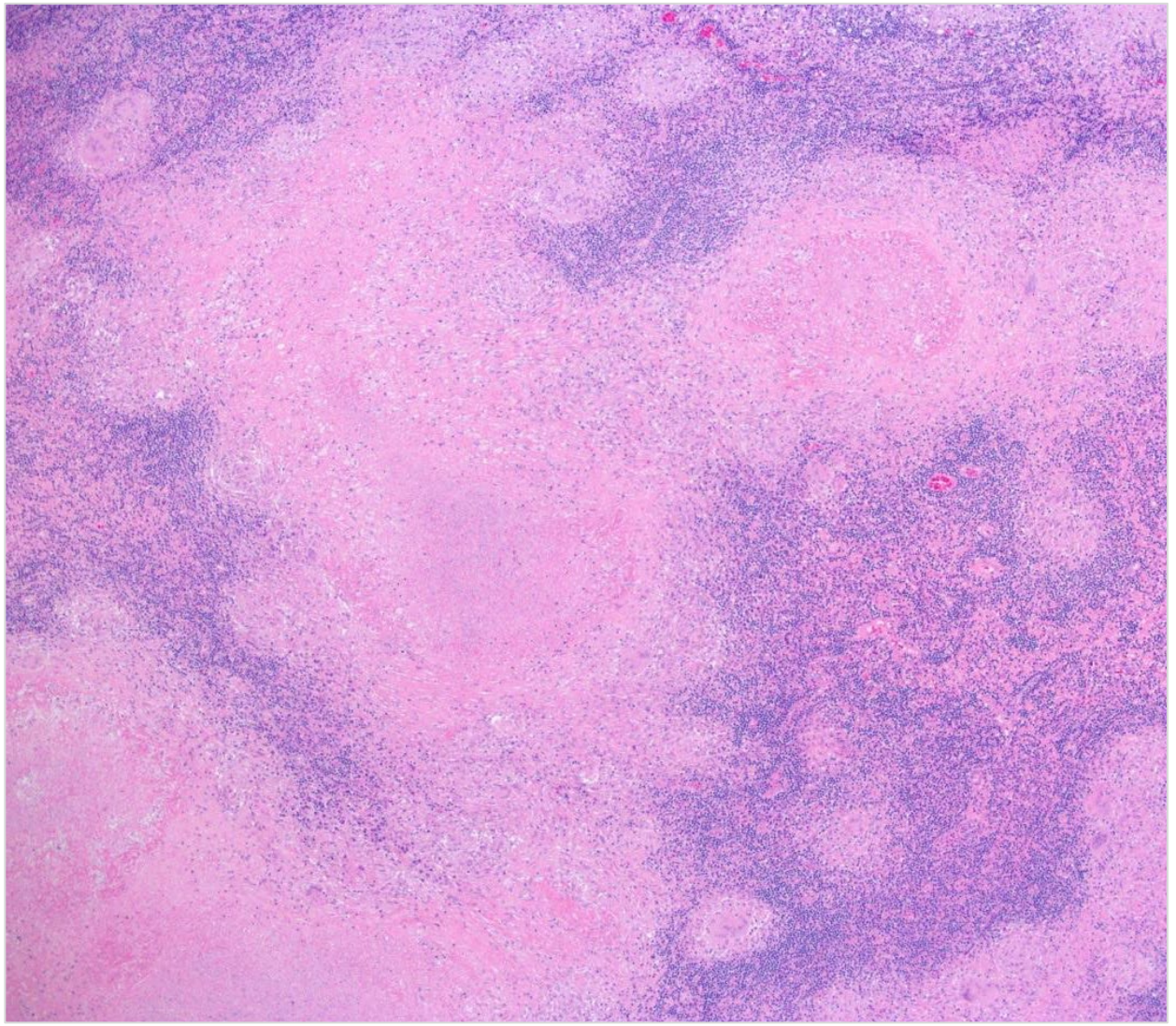




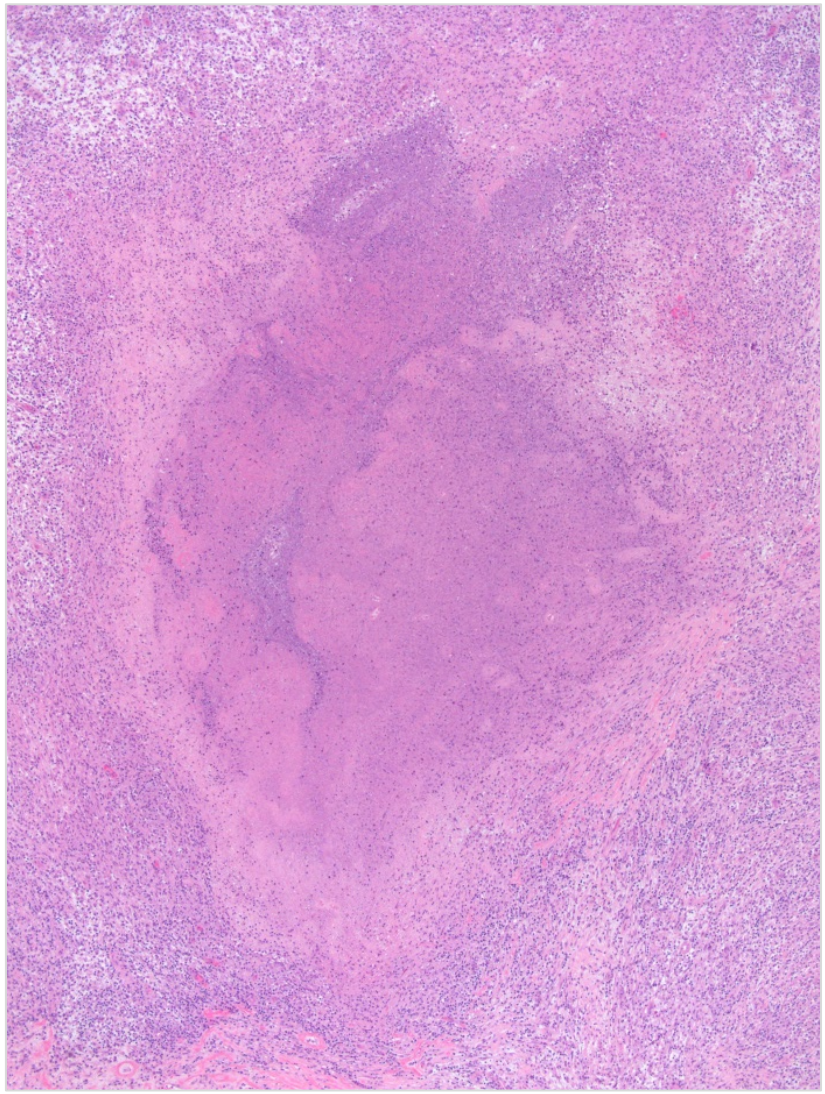
Necrotizing granulomatous inflammation should prompt consideration of infection, until proven otherwise

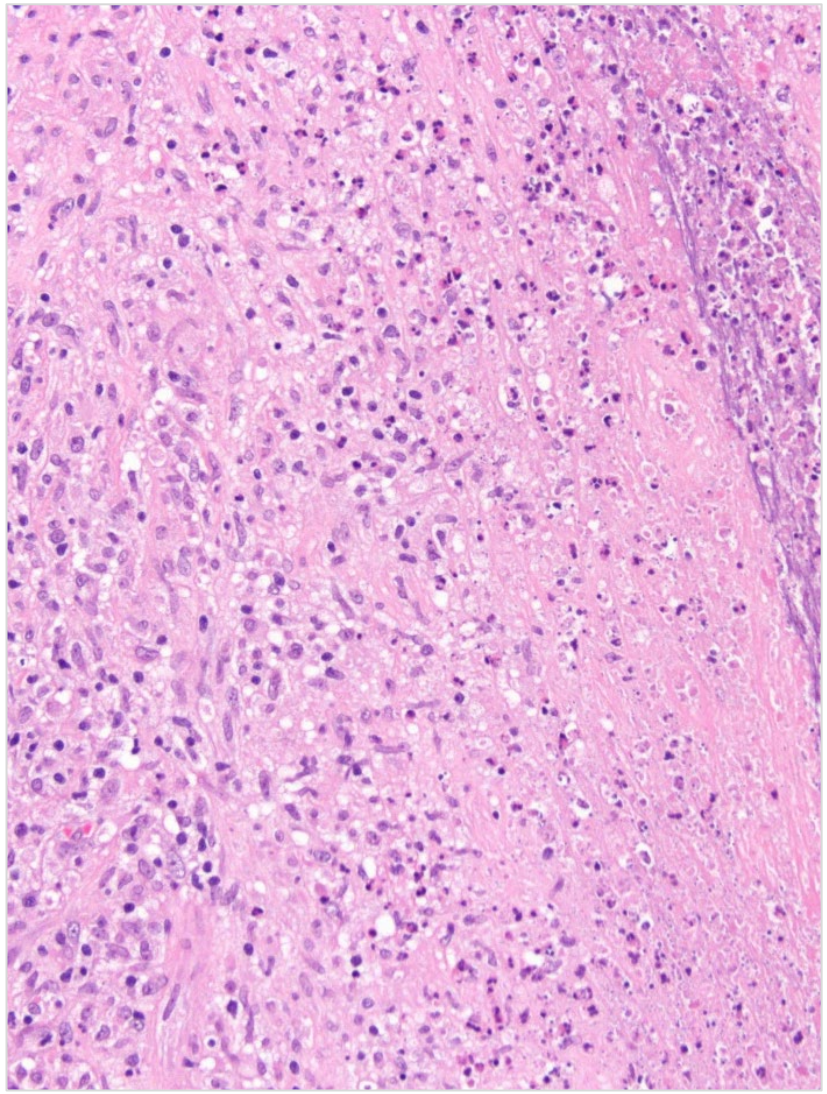
Mycobacterial Meningitis

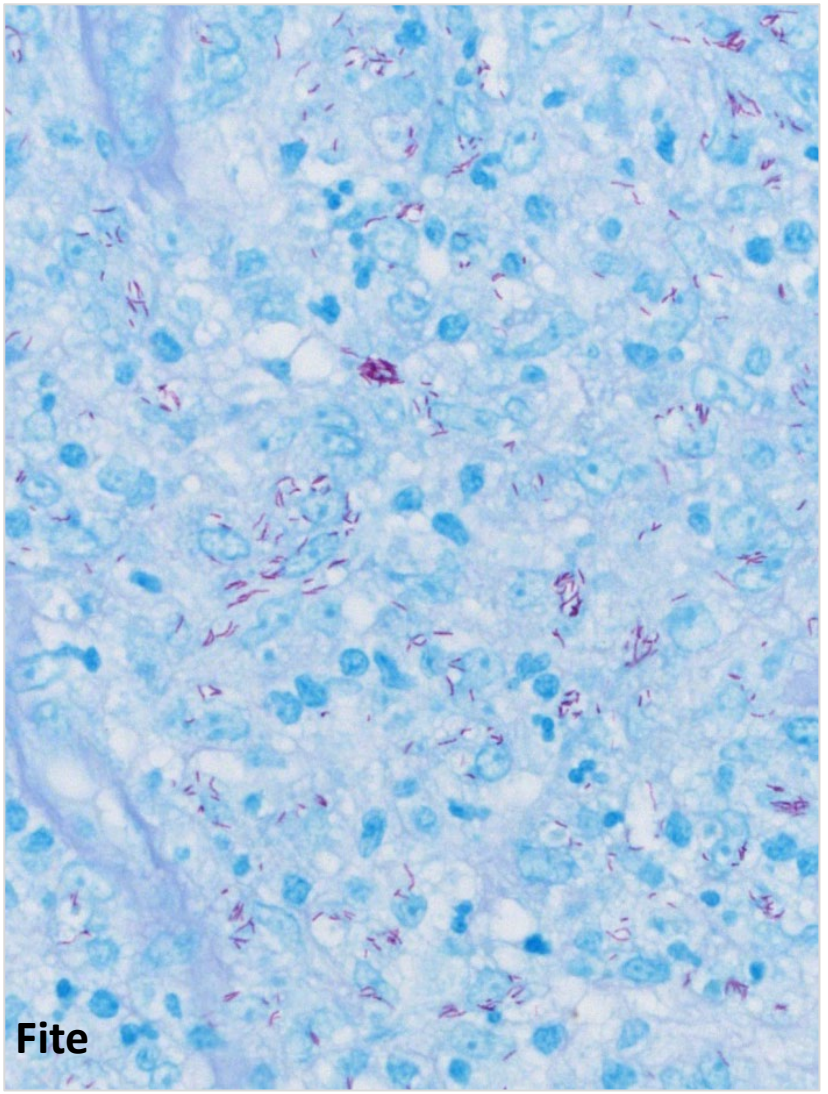




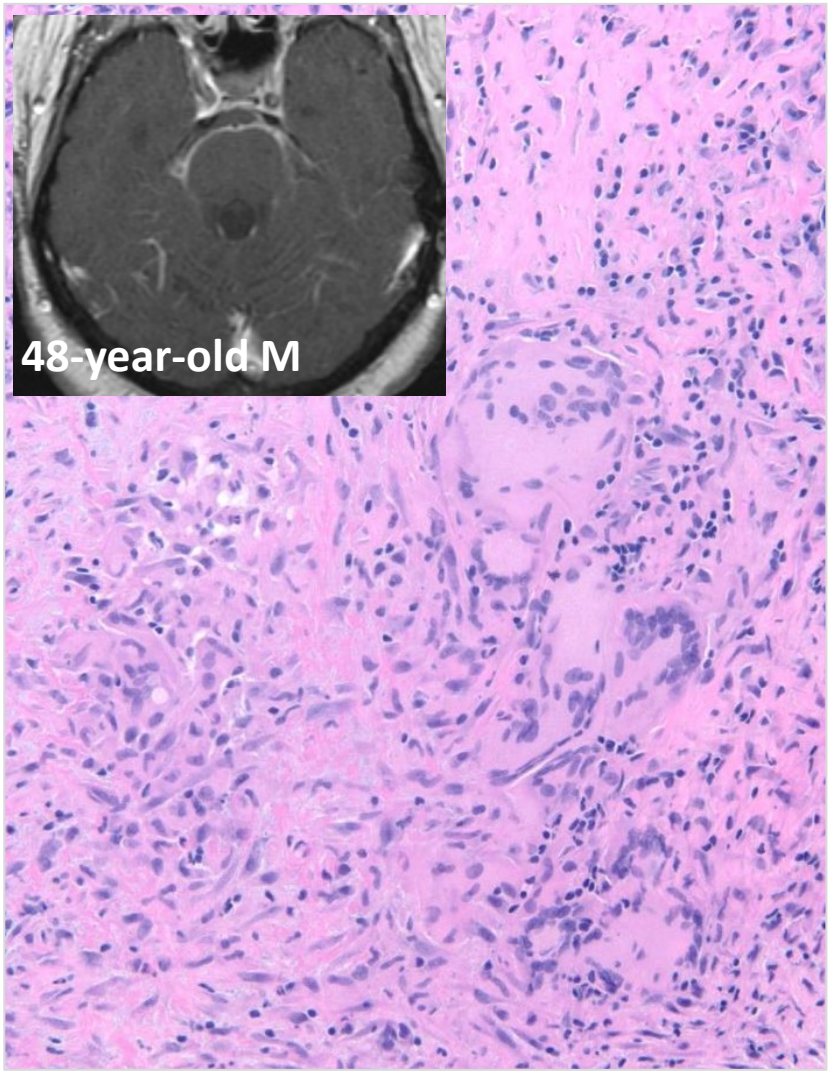
Mycobacterial Meningitis

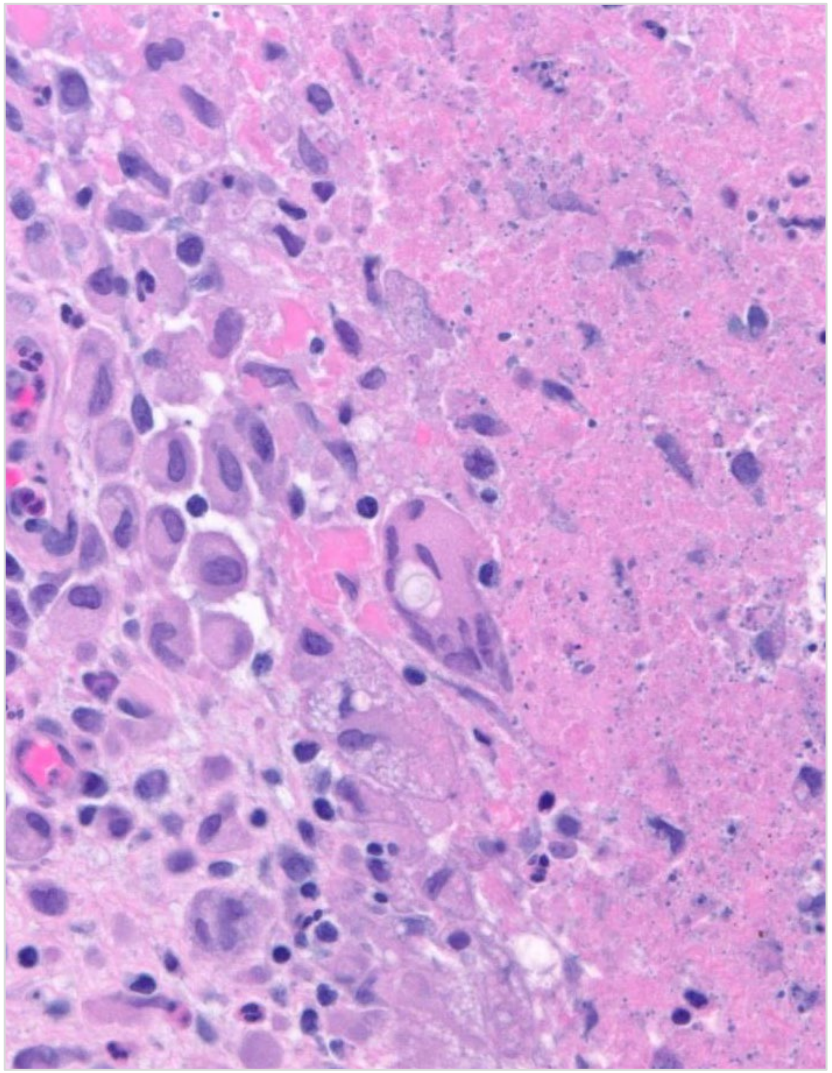


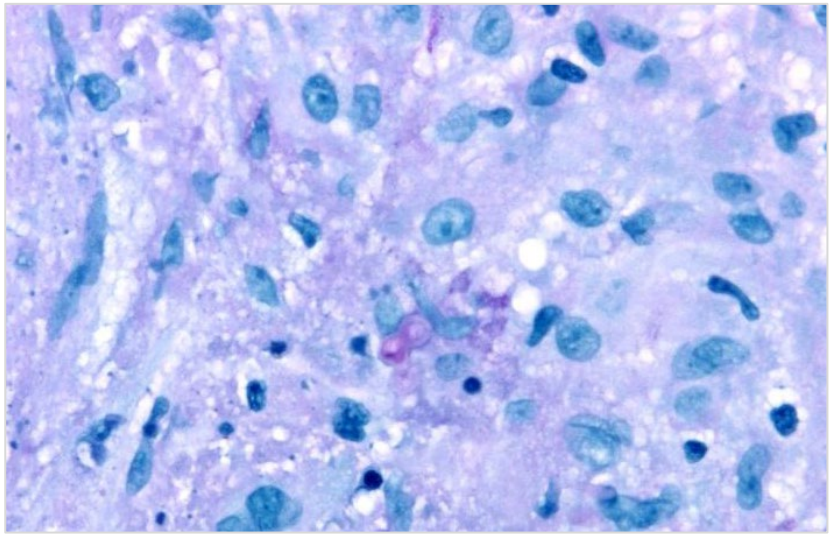


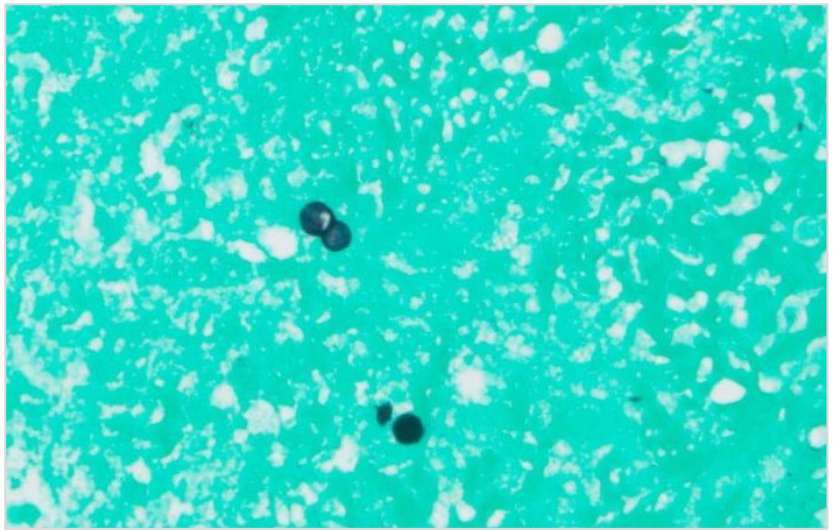


Blastomycosis

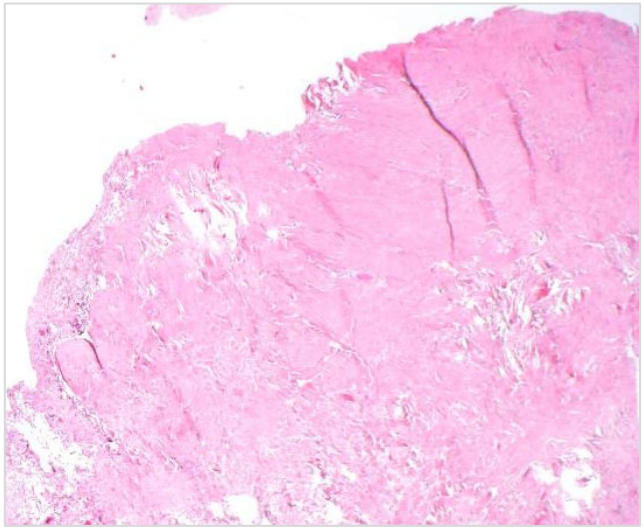


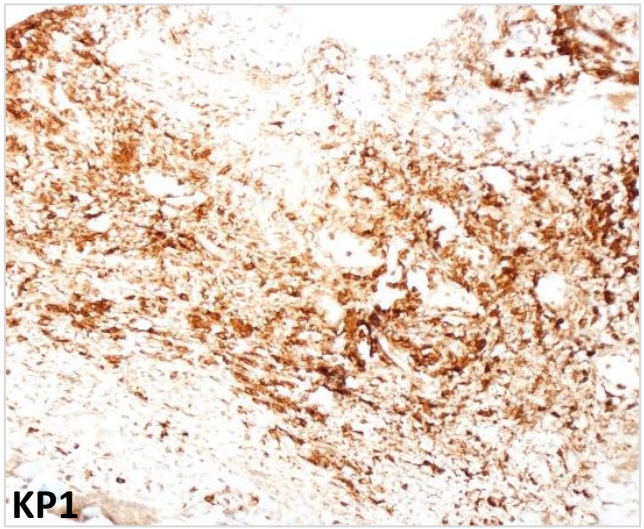


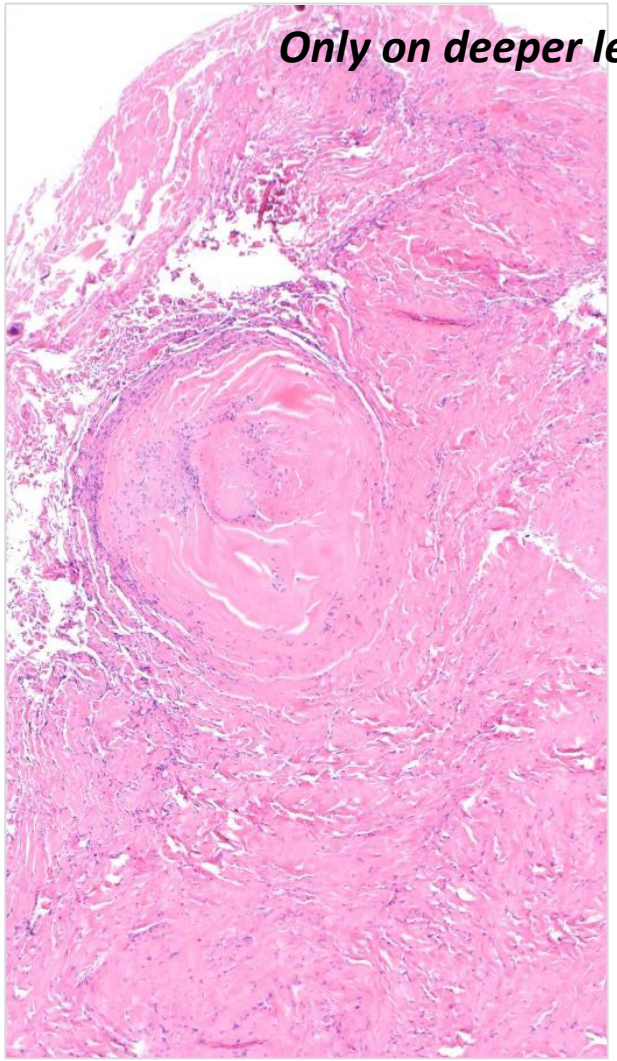


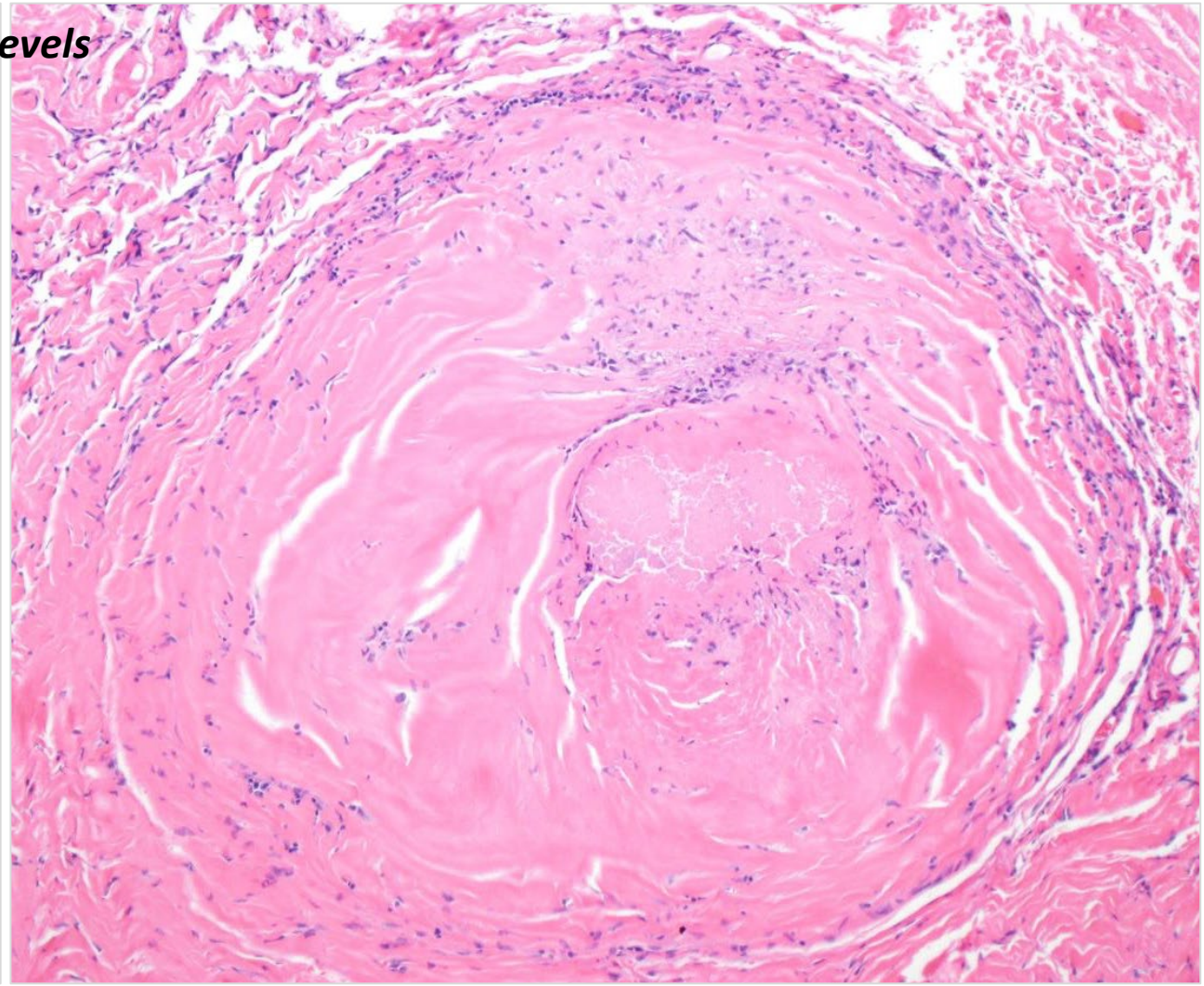


56-year-old with progressive decline & pachymeningitis

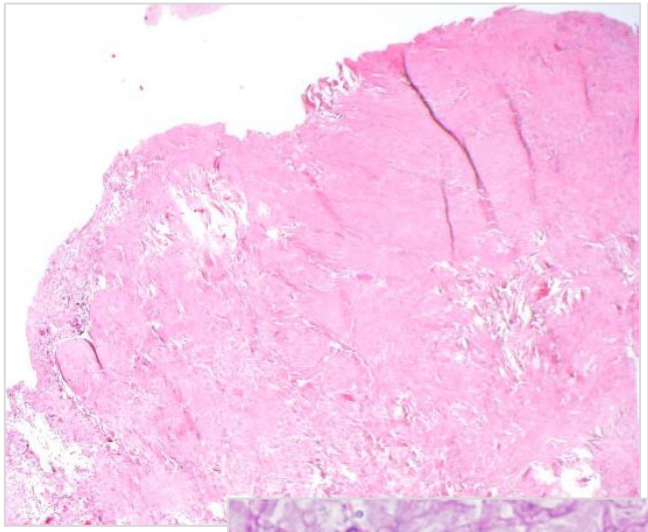


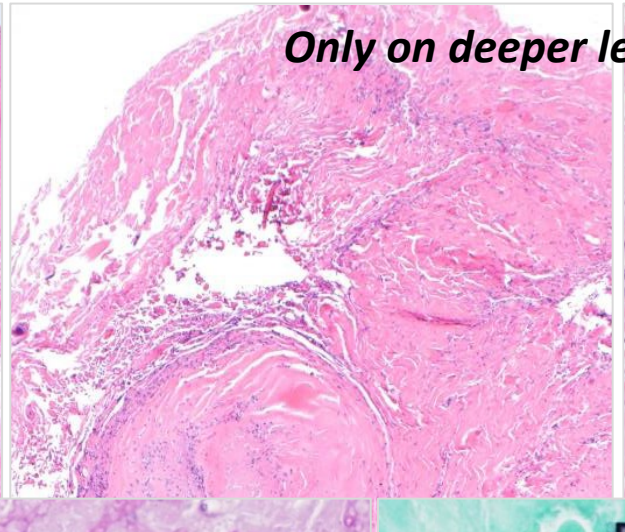


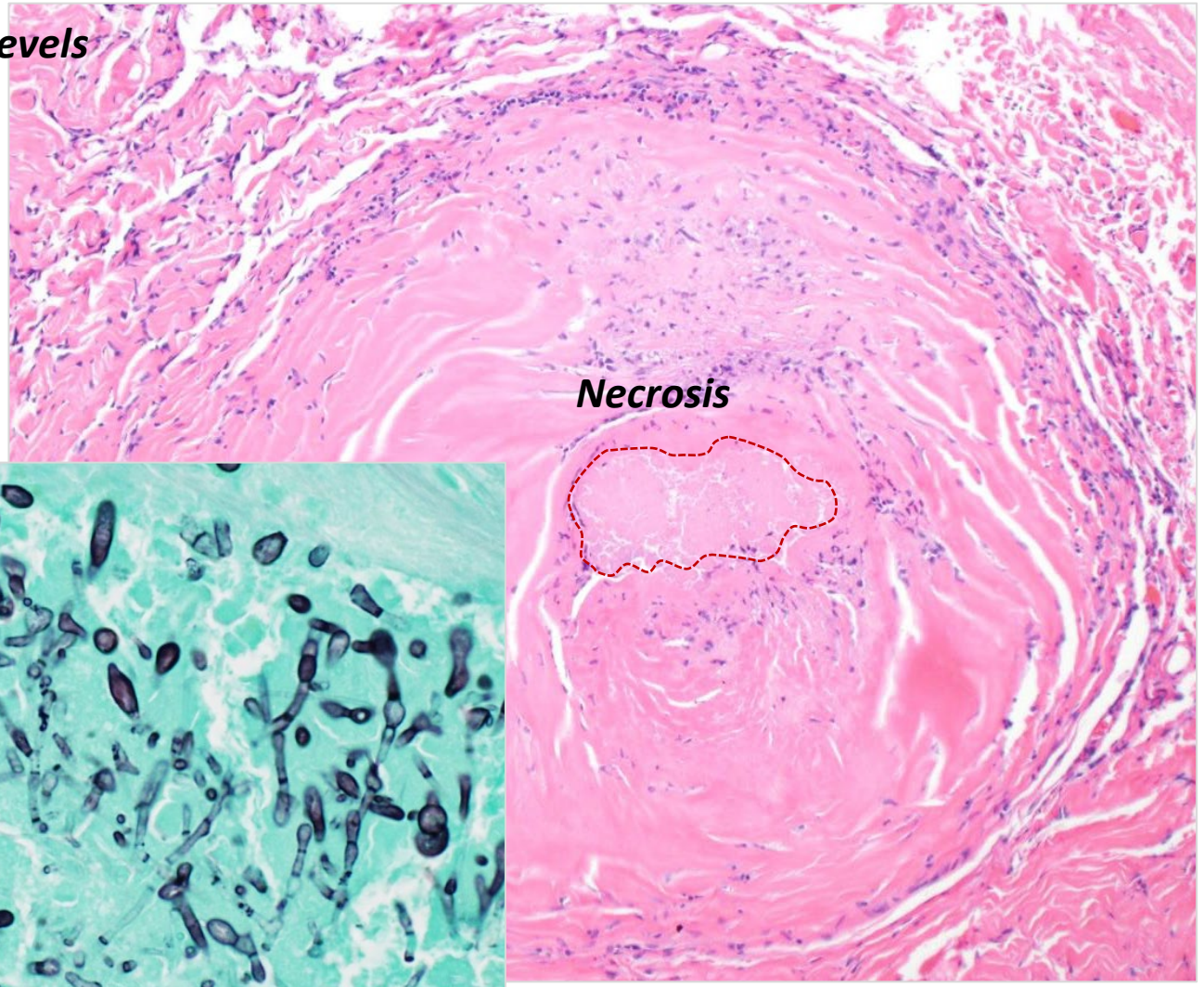


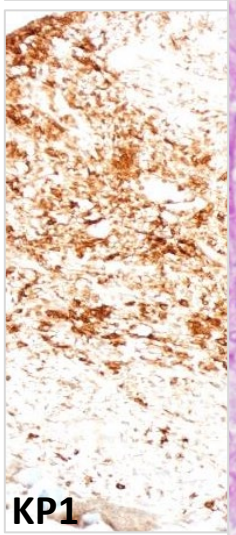


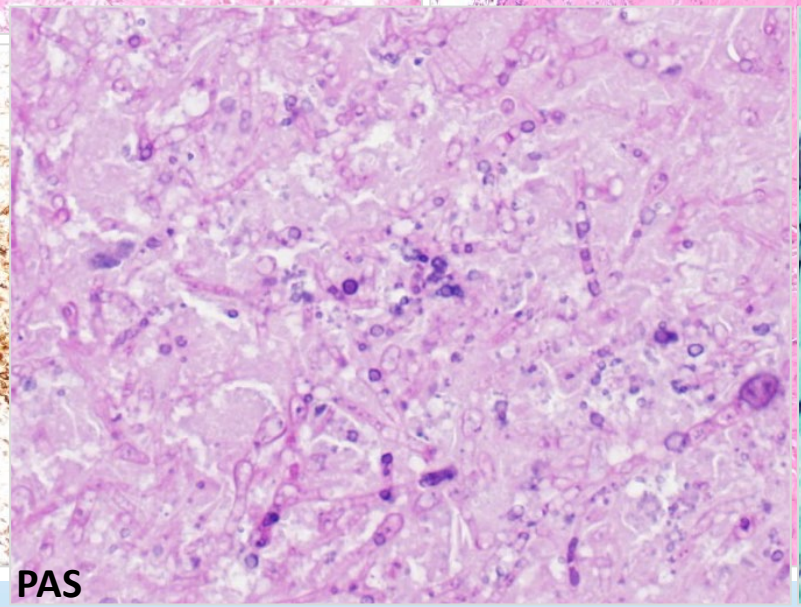
56-year-old with progressive decline & pachymeningitis





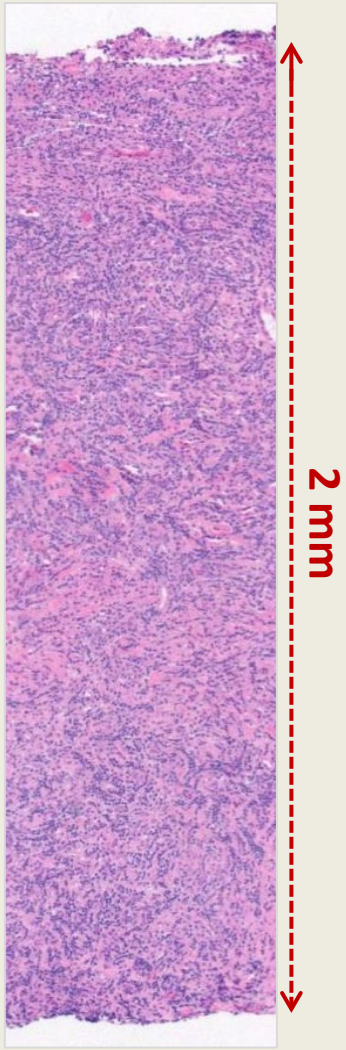


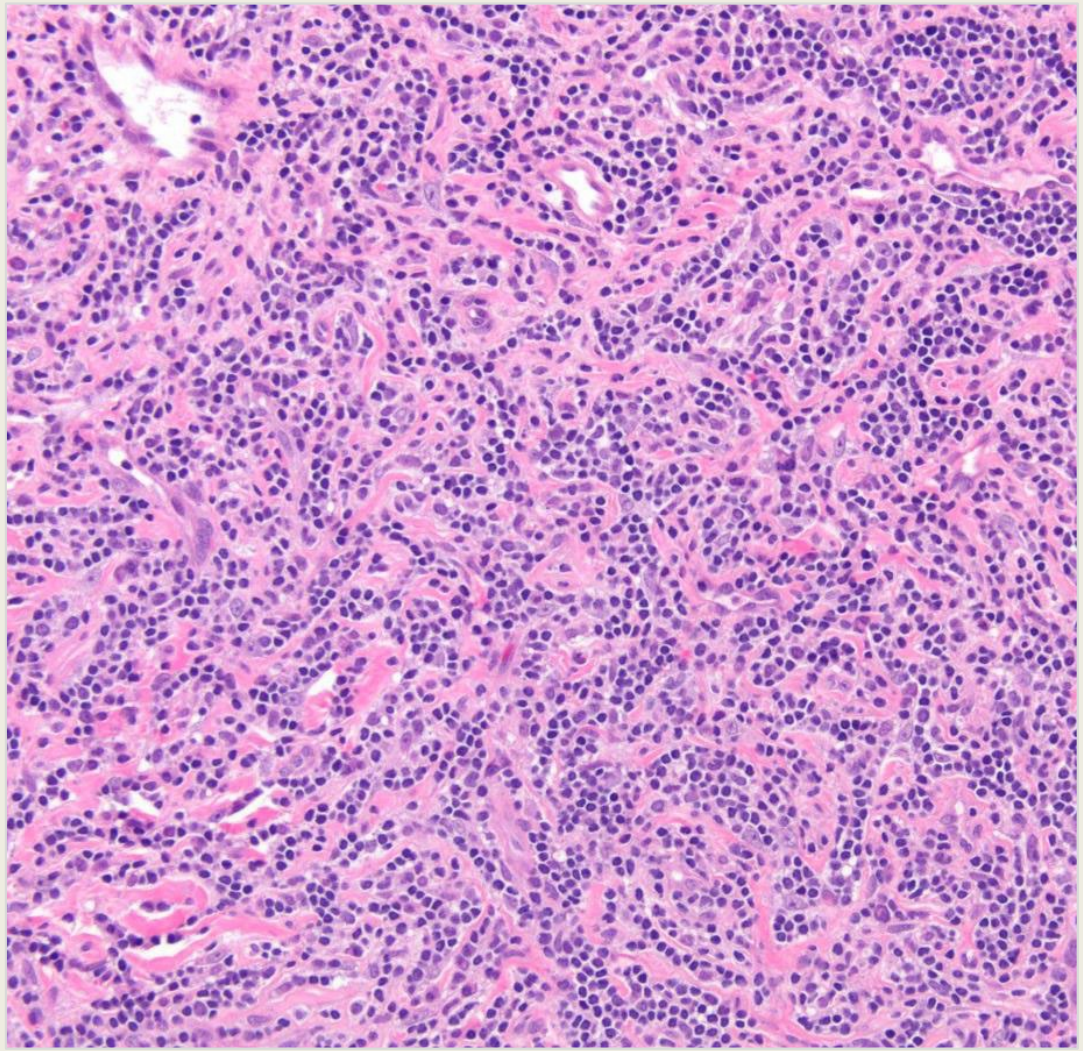


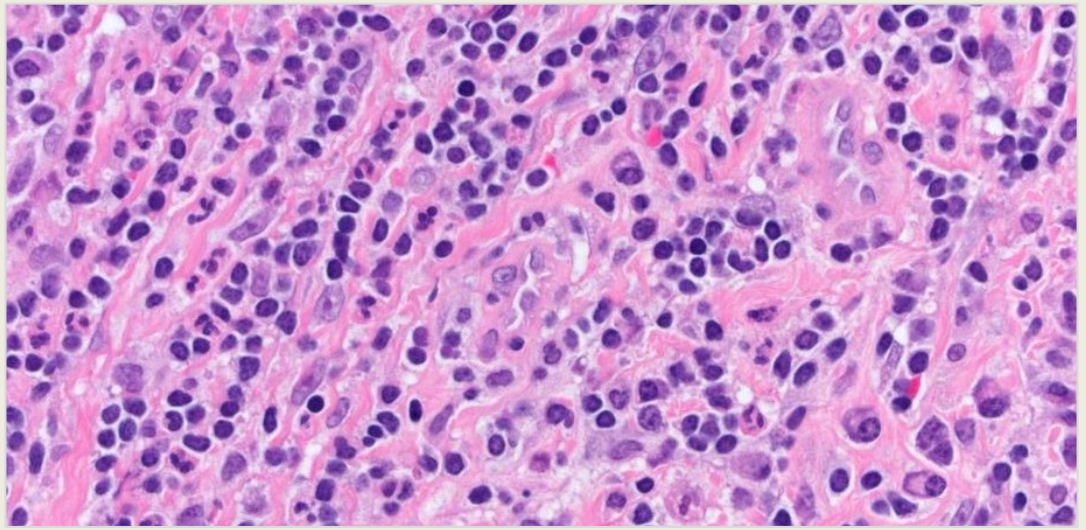


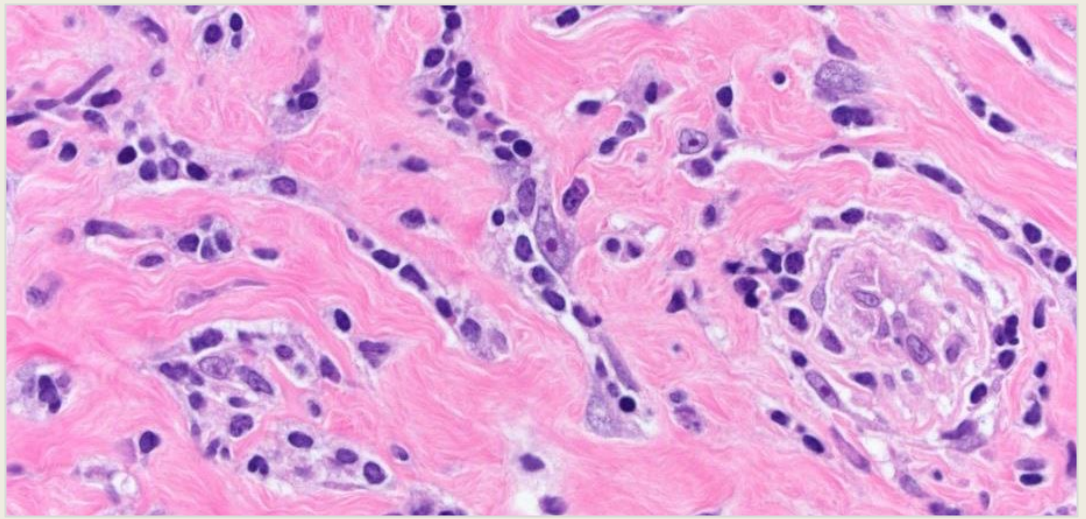
If no cause is found and no specific pathologic finding is present, then it is “idiopathic”

Idiopathic Hypertrophic Pachymeningitis

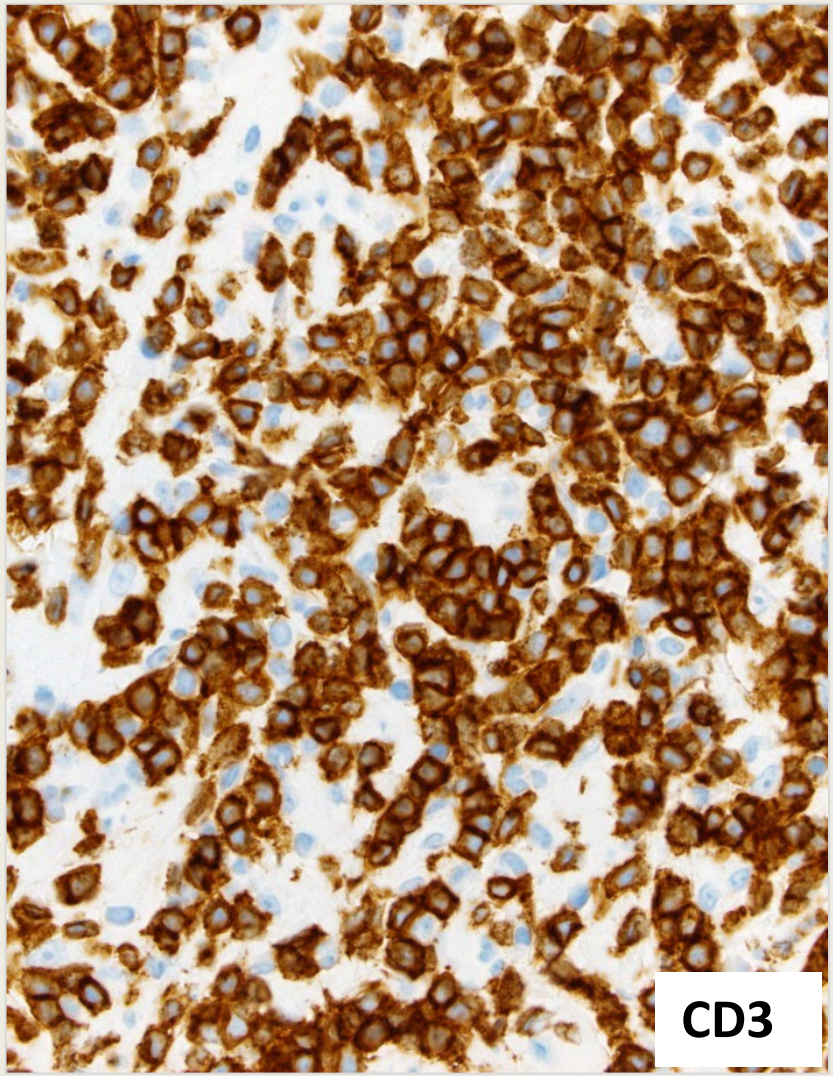


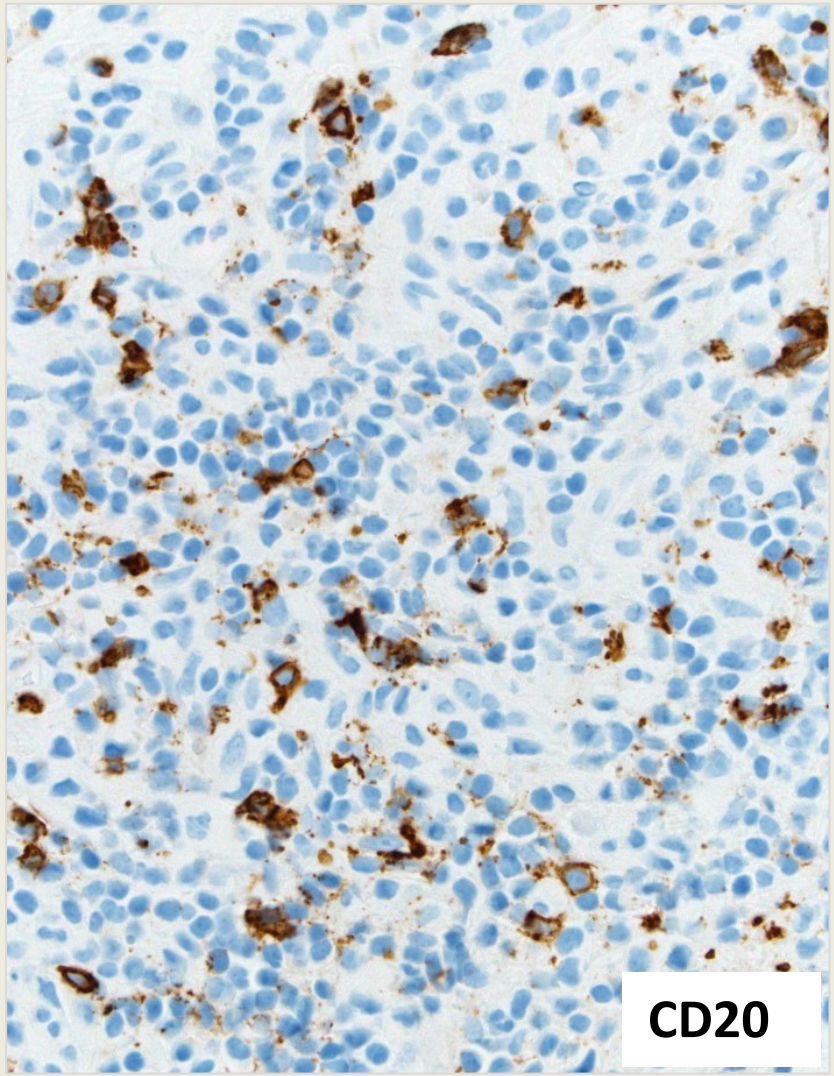


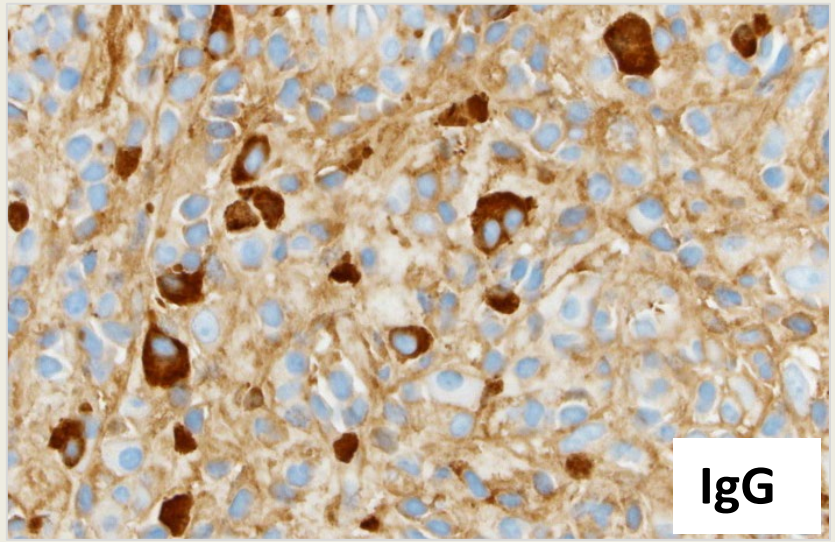


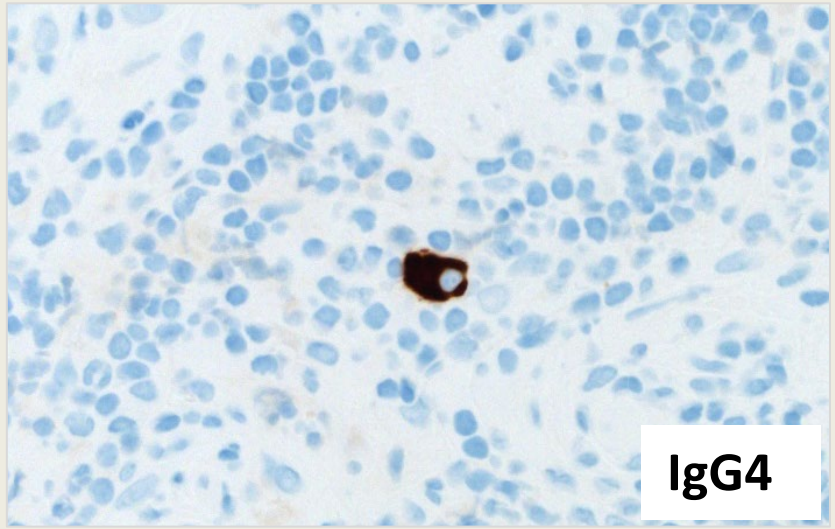


Idiopathic Hypertrophic Pachymeningitis



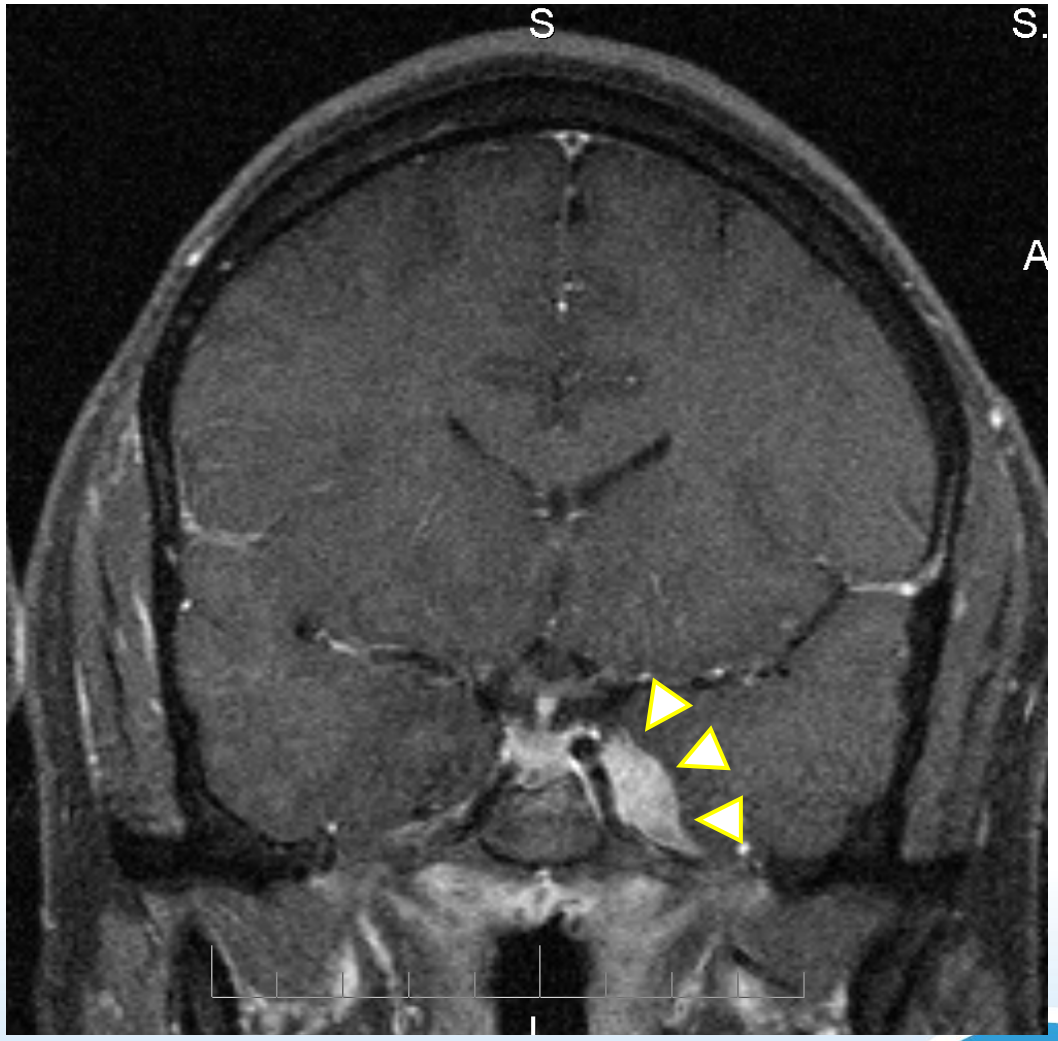




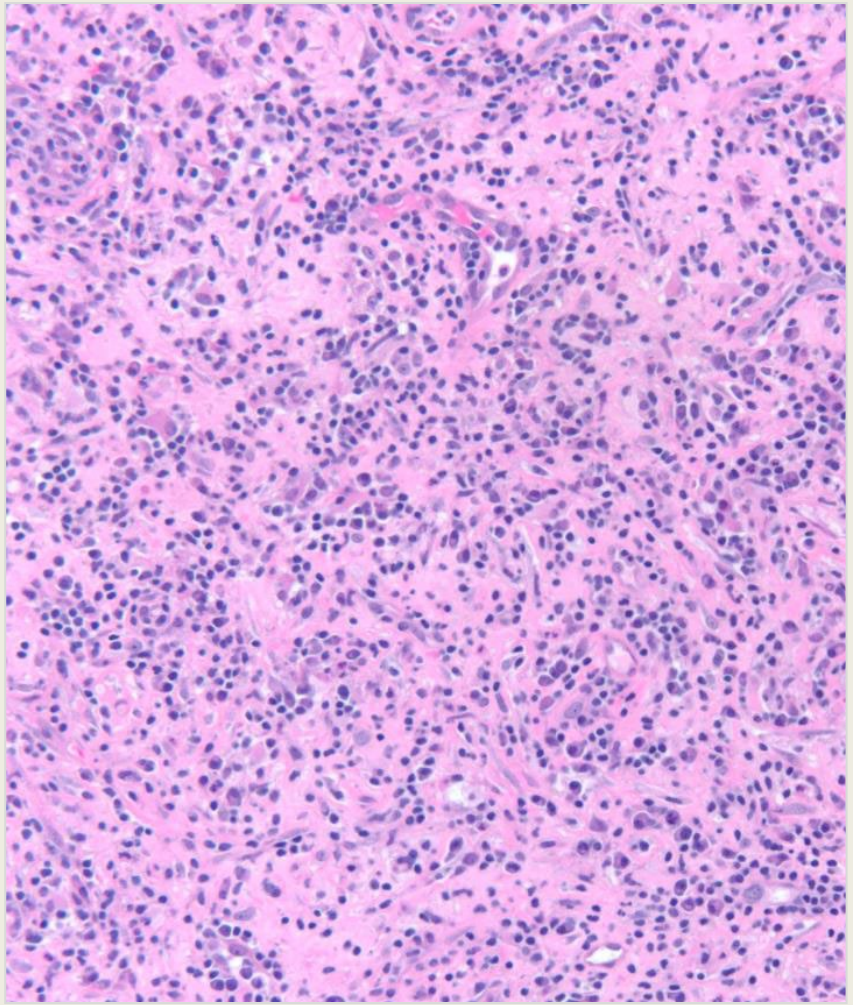


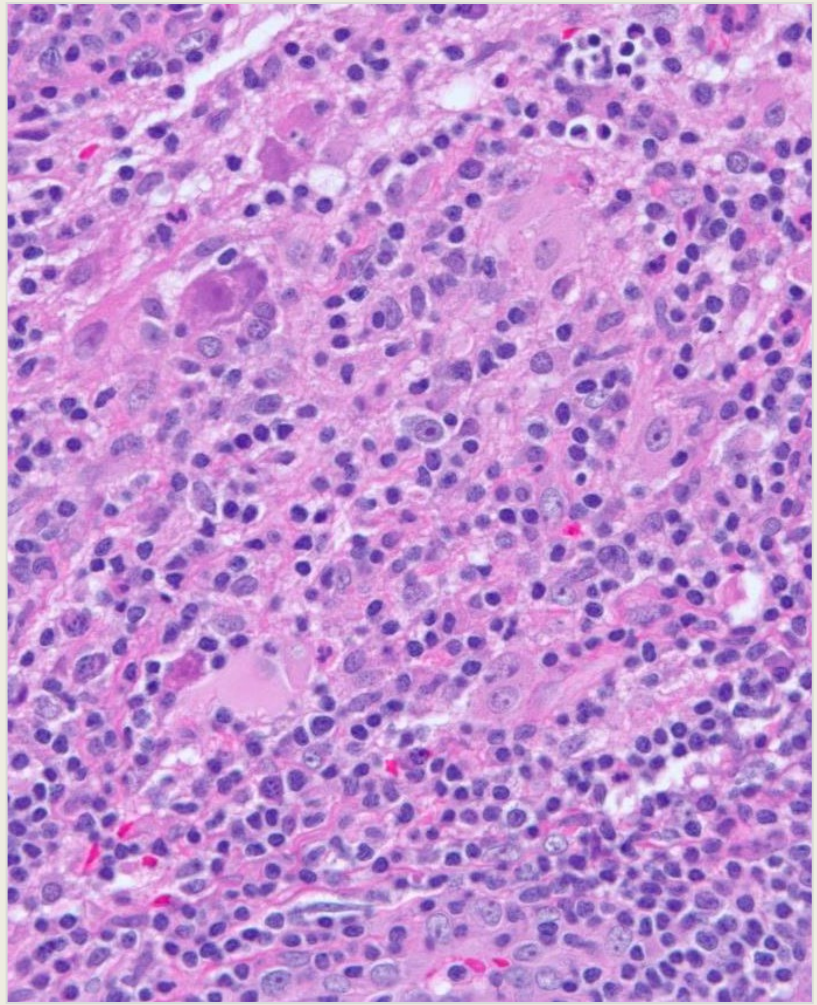
Inflammatory Pseudotumor

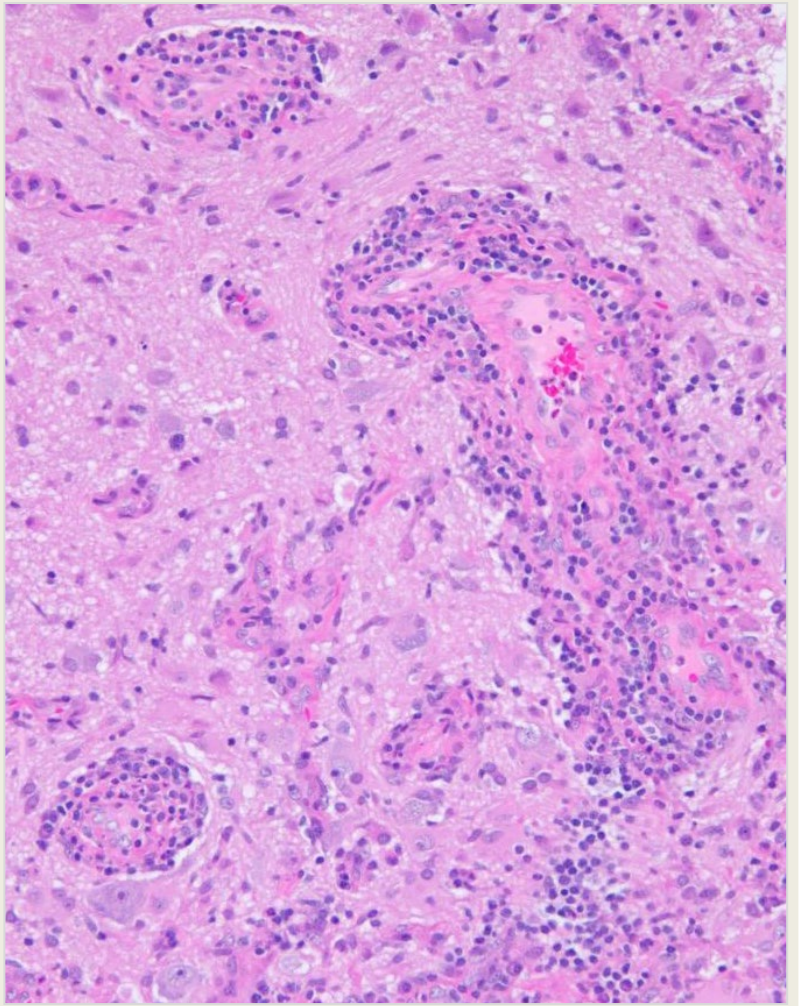
- 30-year-old man
- Decreased left visual acuity and ocular motion
- Left eye pain
- Left cavernous sinus lesion



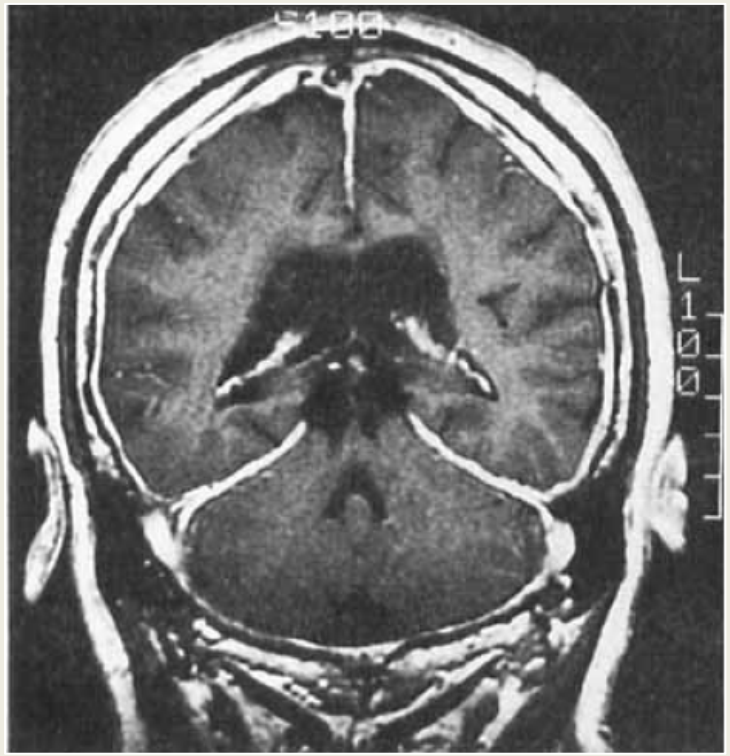
Inflammatory Pseudotumor

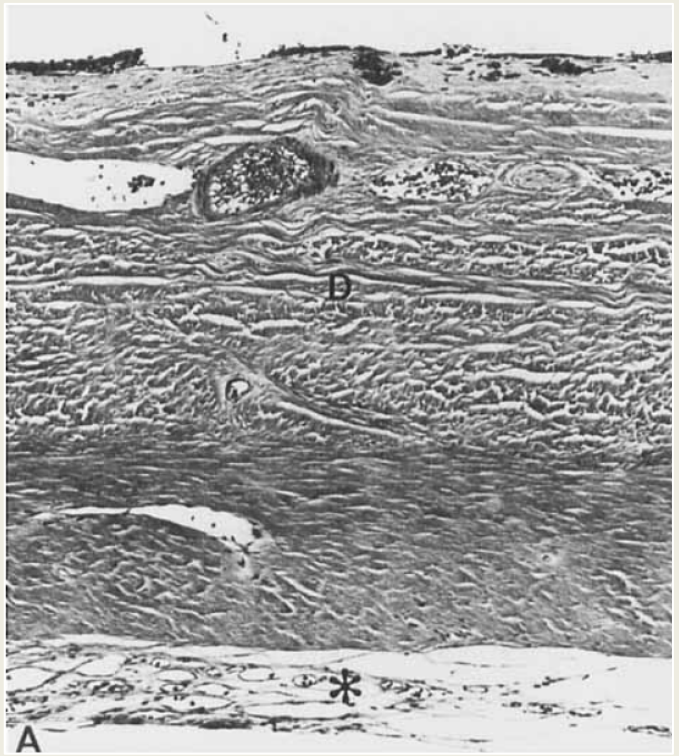


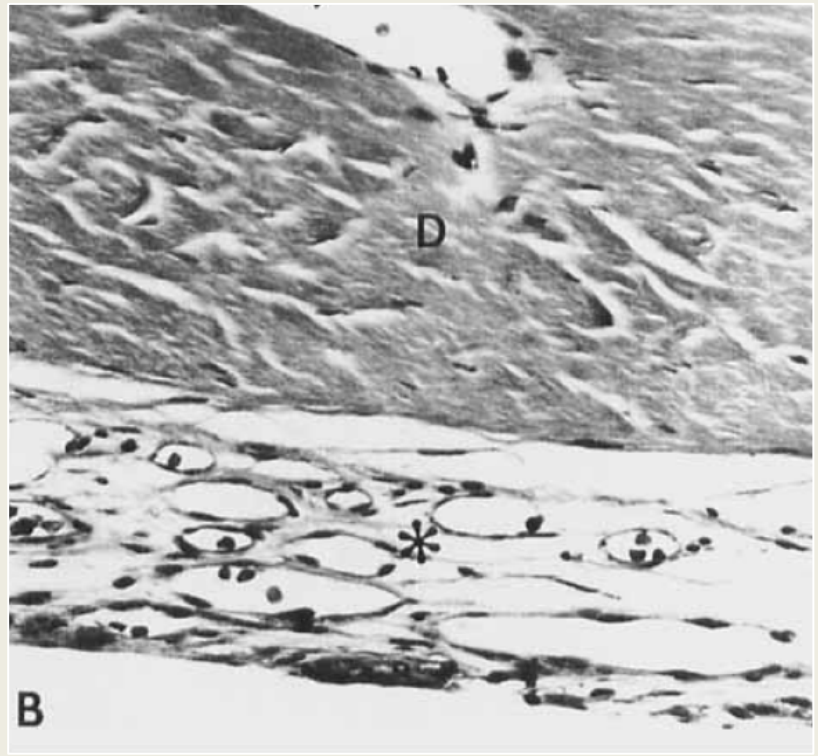




Meningeal biopsy in intracranial hypotension: meningeal enhancement on MRI







Neurology 1995; 45:1801-7

Outline

- Focused discussion of meningeal pathological processes
  - From a Surgical Pathology point of view
  - “meningeal enhancement”
- Inflammatory Meningeal Diseases:
  - IgG4-related disease Infectious
  - Other inflammatory (sarcoid, granulomatosis with polyangiitis)
  - Infectious diseases

Q&A

References

1. Semin Neurol 2014; 34:395-404
2. Mod Pathol. 2012 Sep; 25(9):1181-92
3. Acta Neuropathol 2010; 120:765-76
4. Neuropathology 2016; 36, 93–102
5. Neurology 1995; 45:1801-7