Neuropathology of Central Nervous System Infections

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AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

- Identify the morphological appearances of the various infectious agents that affect the Central Nervous System (CNS).
- Formulate diagnostic hypotheses of CNS infections according to the topography and morphological presentations of the lesions.
- Propose diagnoses of CNS infections taking into account the immunological state of the patient.

Etiology

Bacterial:

Fungal:

Parasitic: Protozoal:

Metazoal (Helminths): Cestodes:

Nematodes:

Trematodes:

Viral:

Etiology

Bacterial: Pyogenic (Gram + / -), Tuberculosis, Syphilis

Fungal: Cryptococcosis, Histoplasmosis, Mucormycosis, Aspergillosis, Paracoccidioidomycosis

Parasitic: Protozoa: Toxoplasmosis, Trypanosomiases, Malaria, Amebiasis

Helminths: Cestodes: Cysticercosis

Nematodes: Strongyloidiasis

Trematodes: Schistosomiasis

Viral: Arboviroses (Dengue, Zika), CMV, Herpes, HIV, HTLV1, Measles, Poliomyelitis, PML, Rabies.

Morphological Presentations of the Lesions

- Meningitis
- Encephalitis/Myelitis (Polio, Leuko)
- Encephalopathy/Myelopathy

- Space occupying lesions “Pseudo-tumors”
  - Abscesses
  - Granulomatous lesions
  - Non-granulomatous (necrotizing) lesions
  - Cystic lesions
  - Calcified lesions

- Vasculitis/Infarct/Hemorrhage

- Congenital Infections / Malformations

Morphological Presentations x Etiology x Host

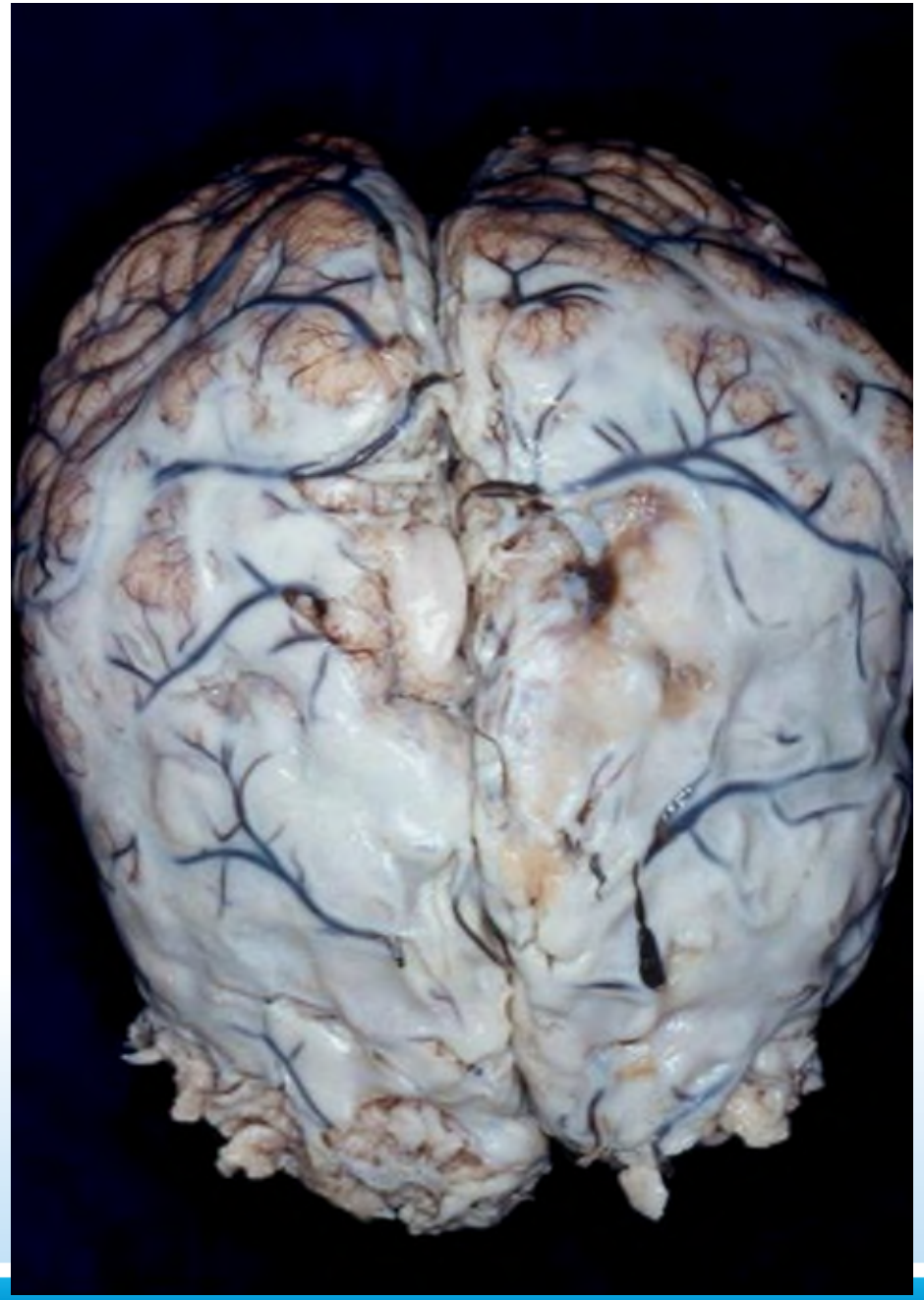
One single agent can present with various morphological patterns
(e.g. Tuberculosis, Toxoplasmosis, Cryptococcosis).

Relationship with the immunological state of the host
(e.g. Cryptococcosis, Toxoplasmosis, Tuberculosis).

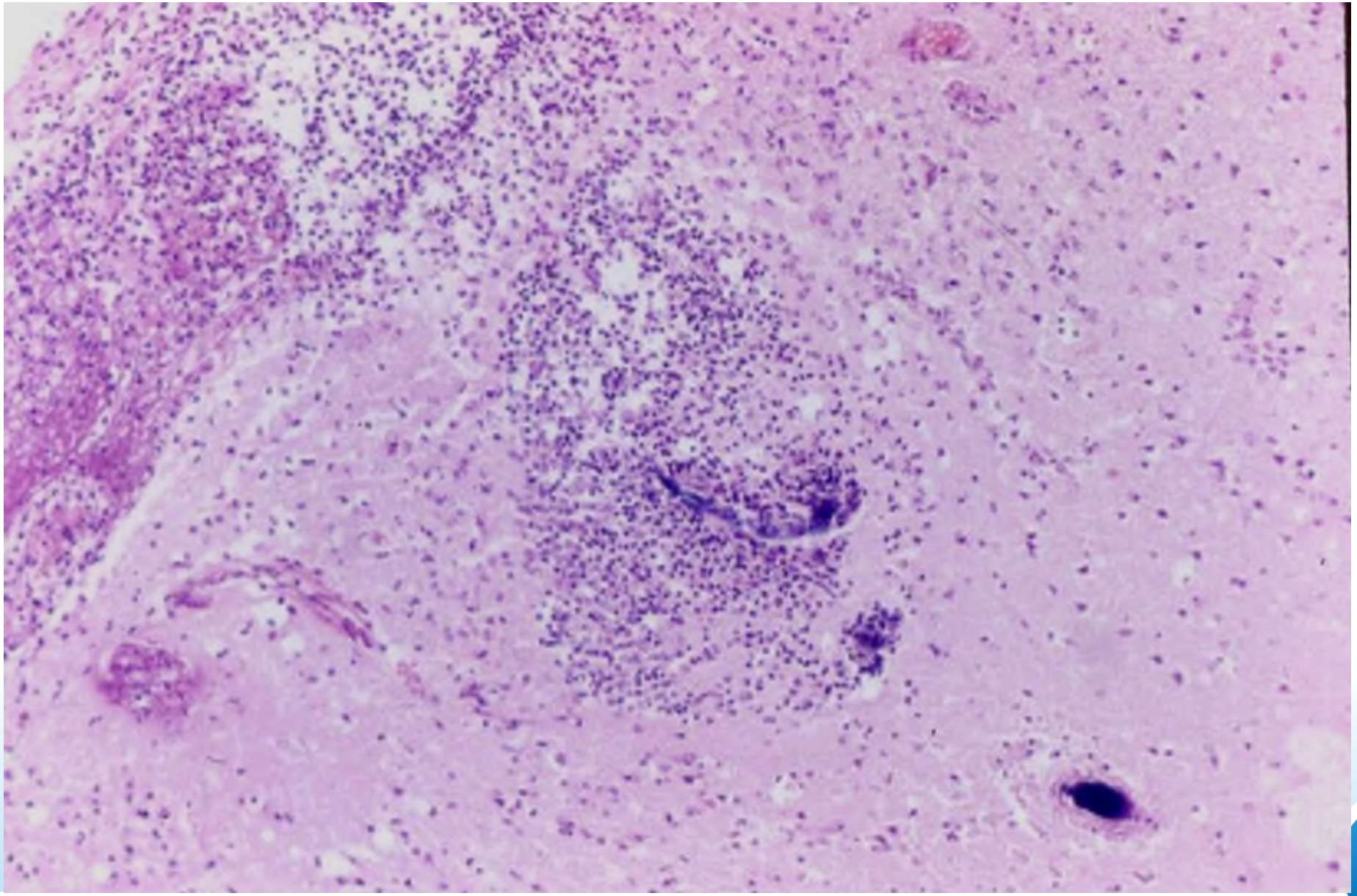
Relationship with the age of the host (e.g. etiology of bacterial meningitis).

Acute, sub-acute, chronic, post-infectious
(e.g. Pyogenic, Dengue, Measles…)

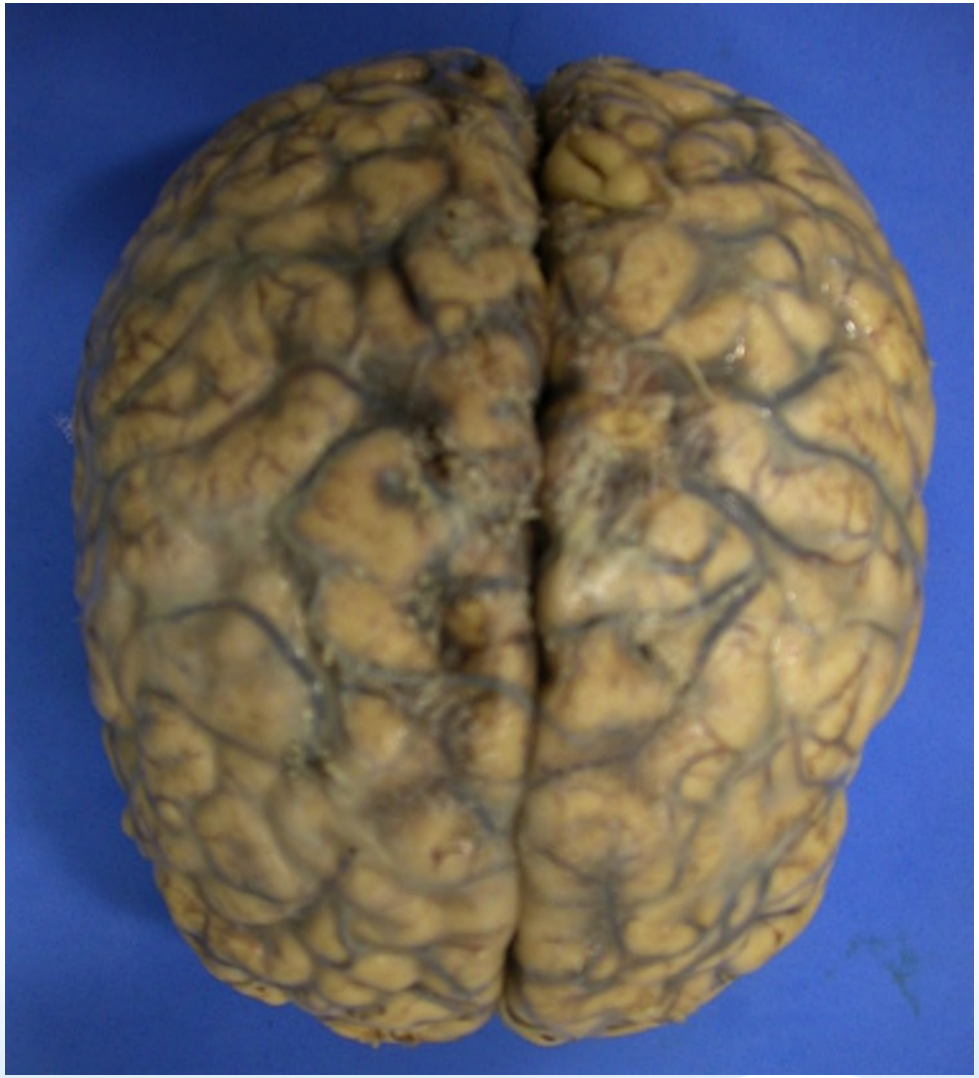
Neisseria meningitidis (Gram -) Hyper acute meningitis
Waterhouse-Friderichsen syndrome




HC. 217/94



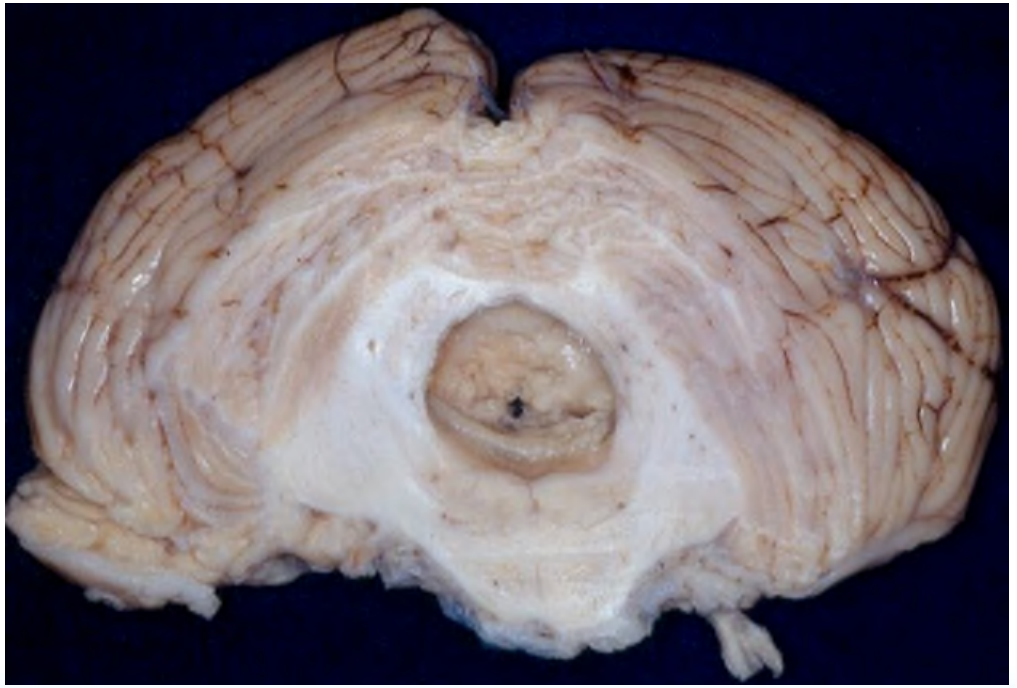
Sub-acute / Chronic stages



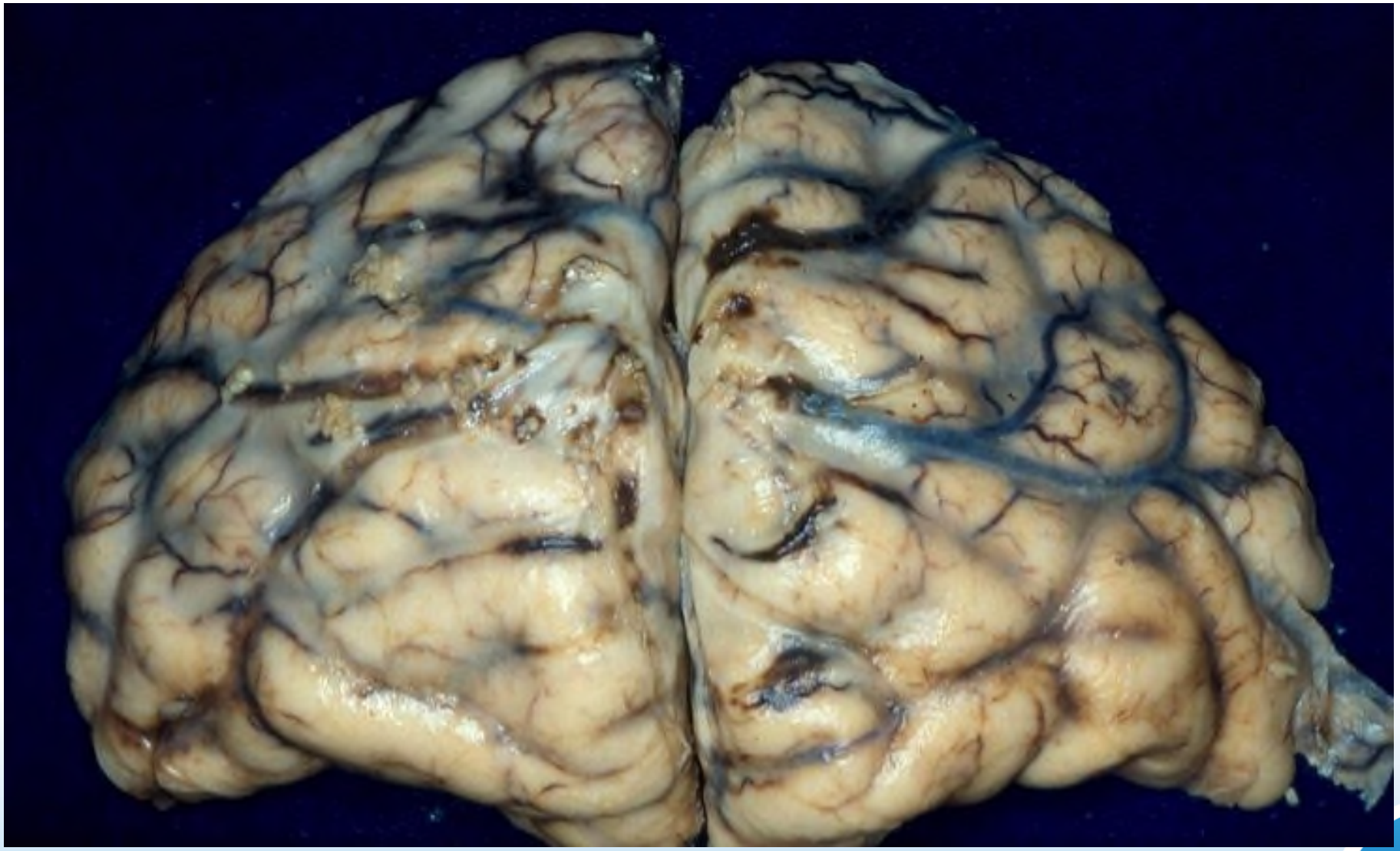
COMPLICATIONS

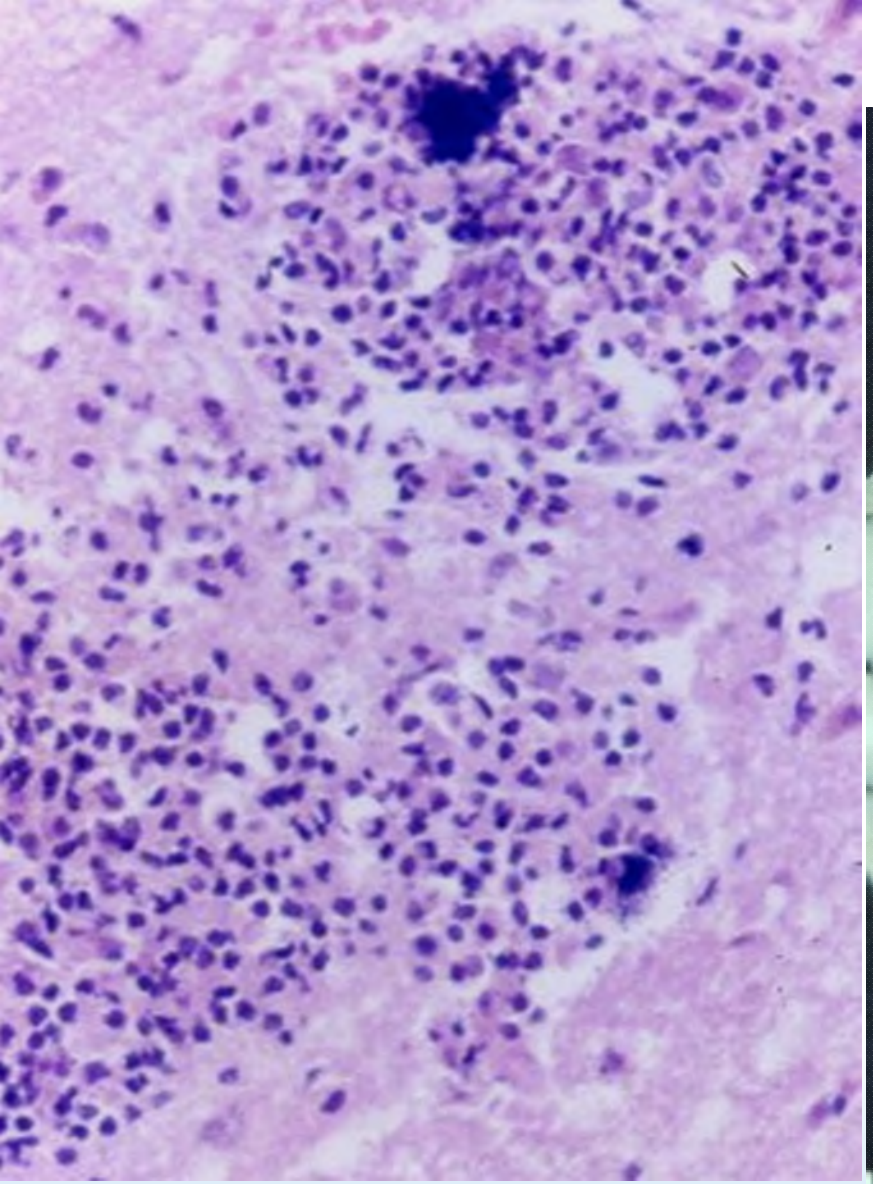
- Ventriculitis
- Hydrocephalus
- Infarct (vasculitis, thrombosis)
- Abscess (micro-abscesses)

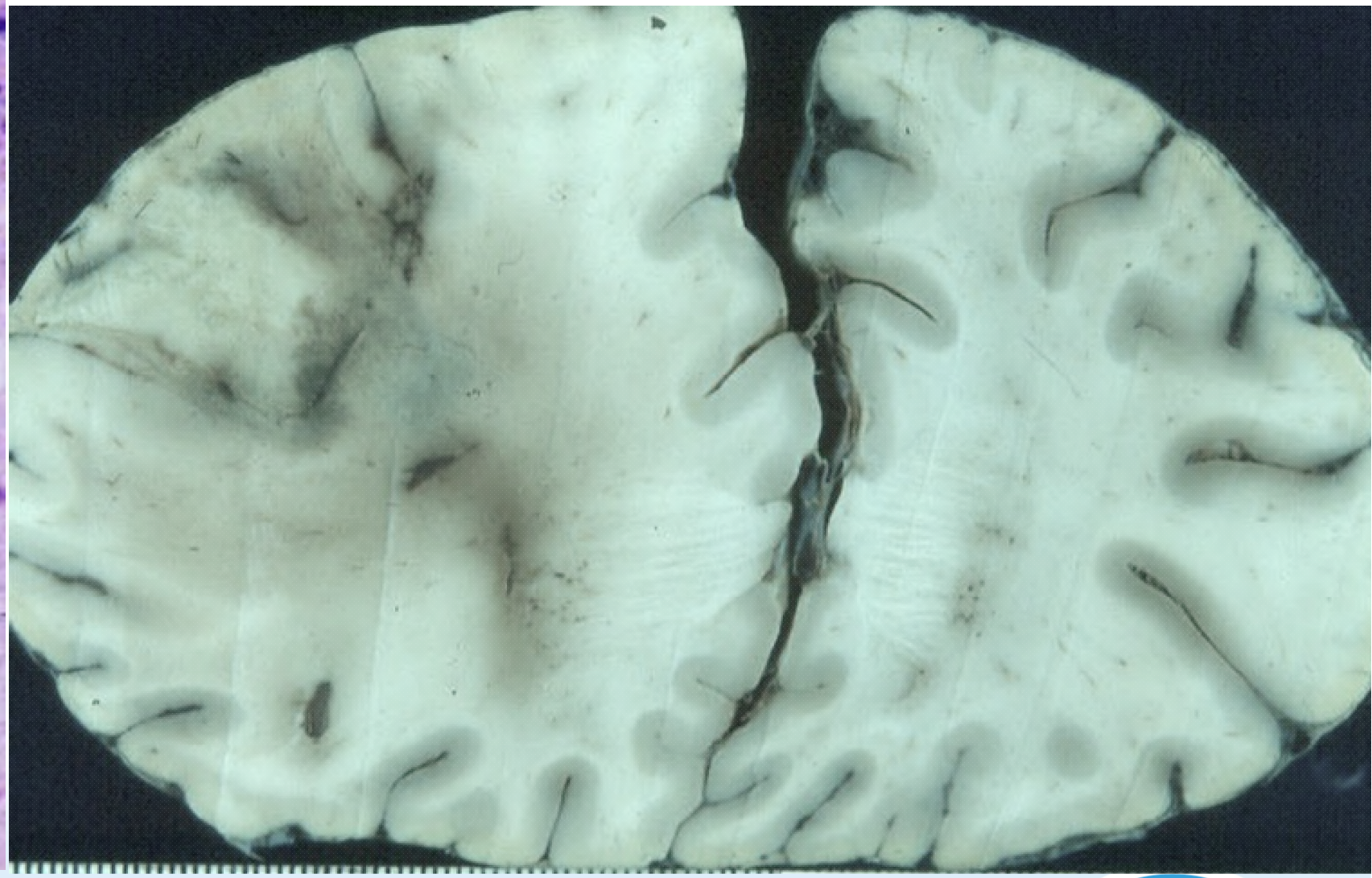
Ventriculitis, hydrocephalus



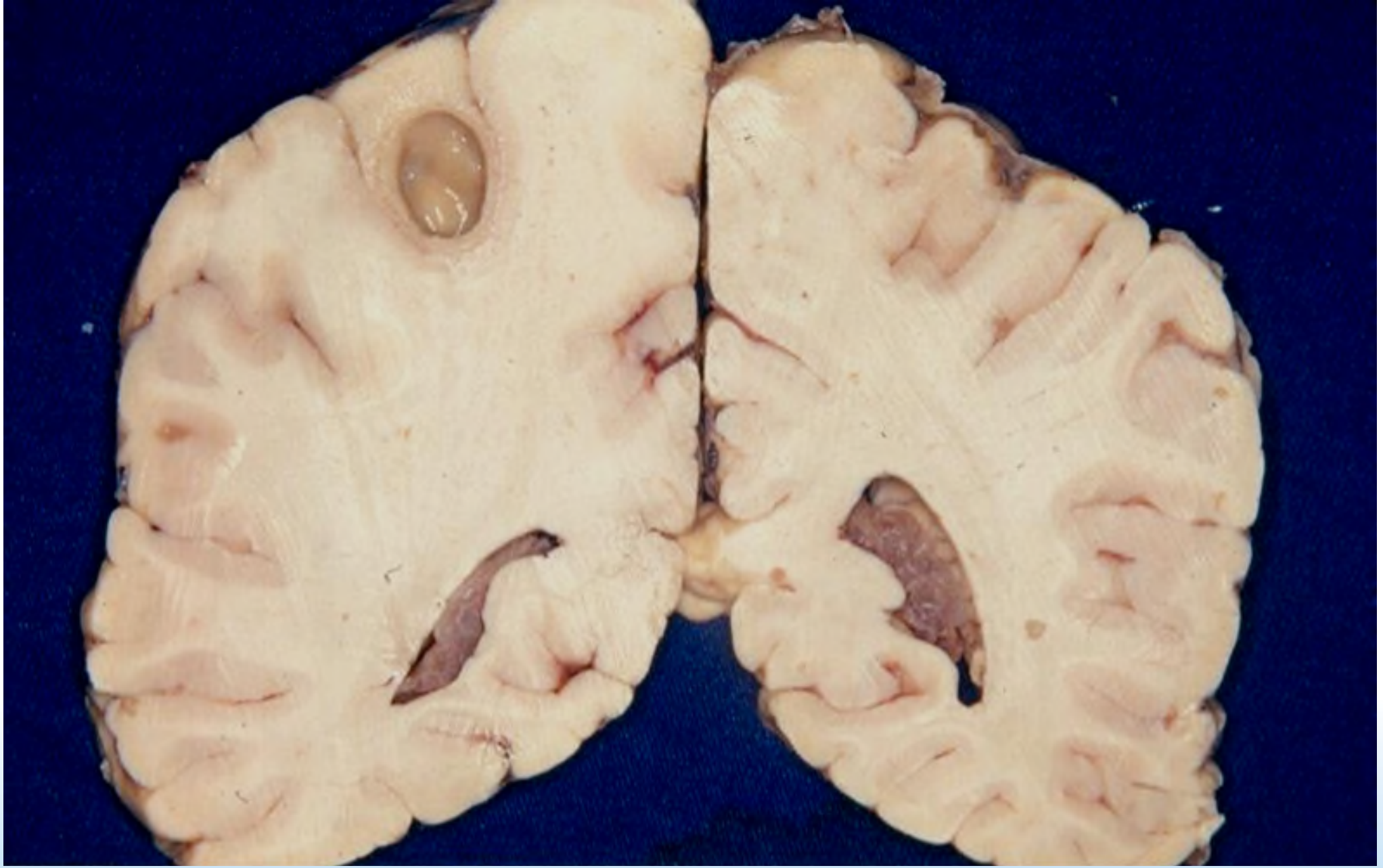
Venous congestion, inflammation, may cause thrombosis and venous infarct







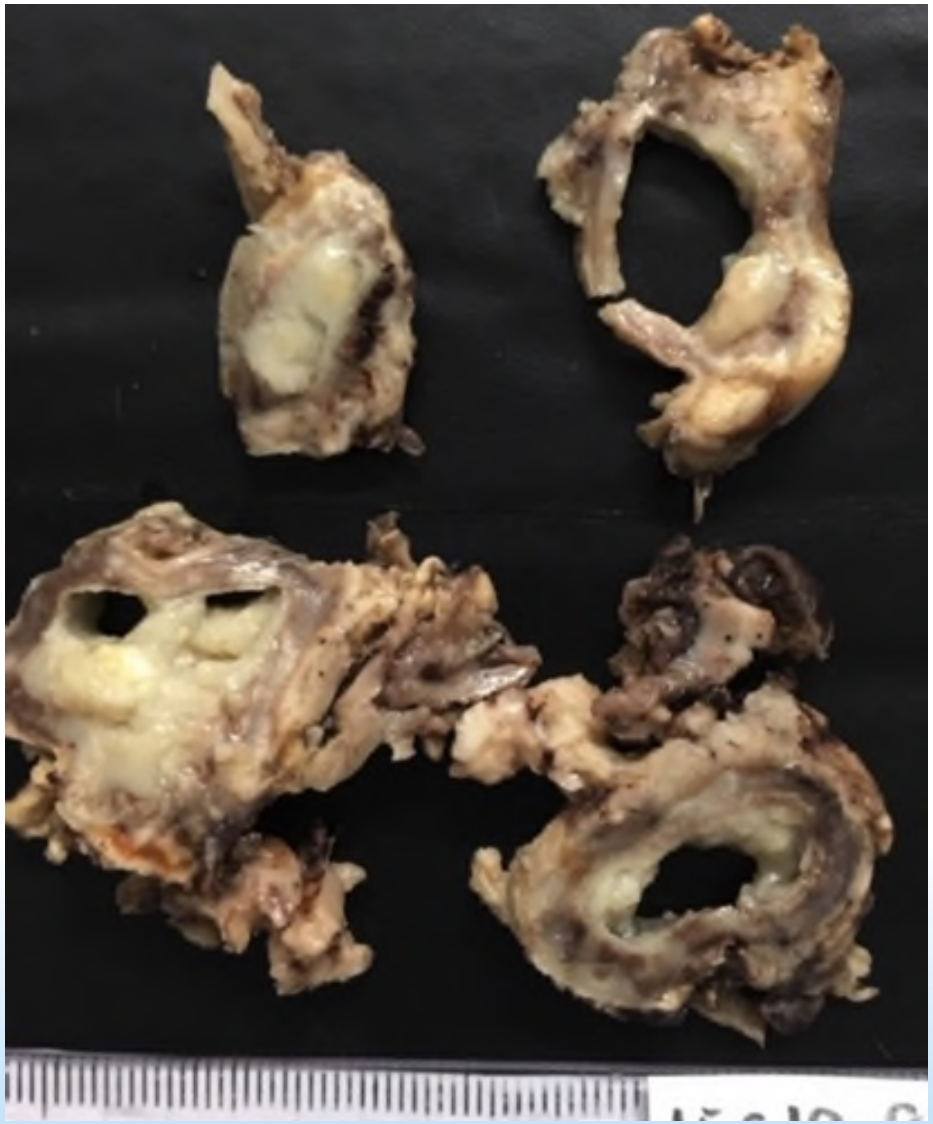
Microabscess and large abscess

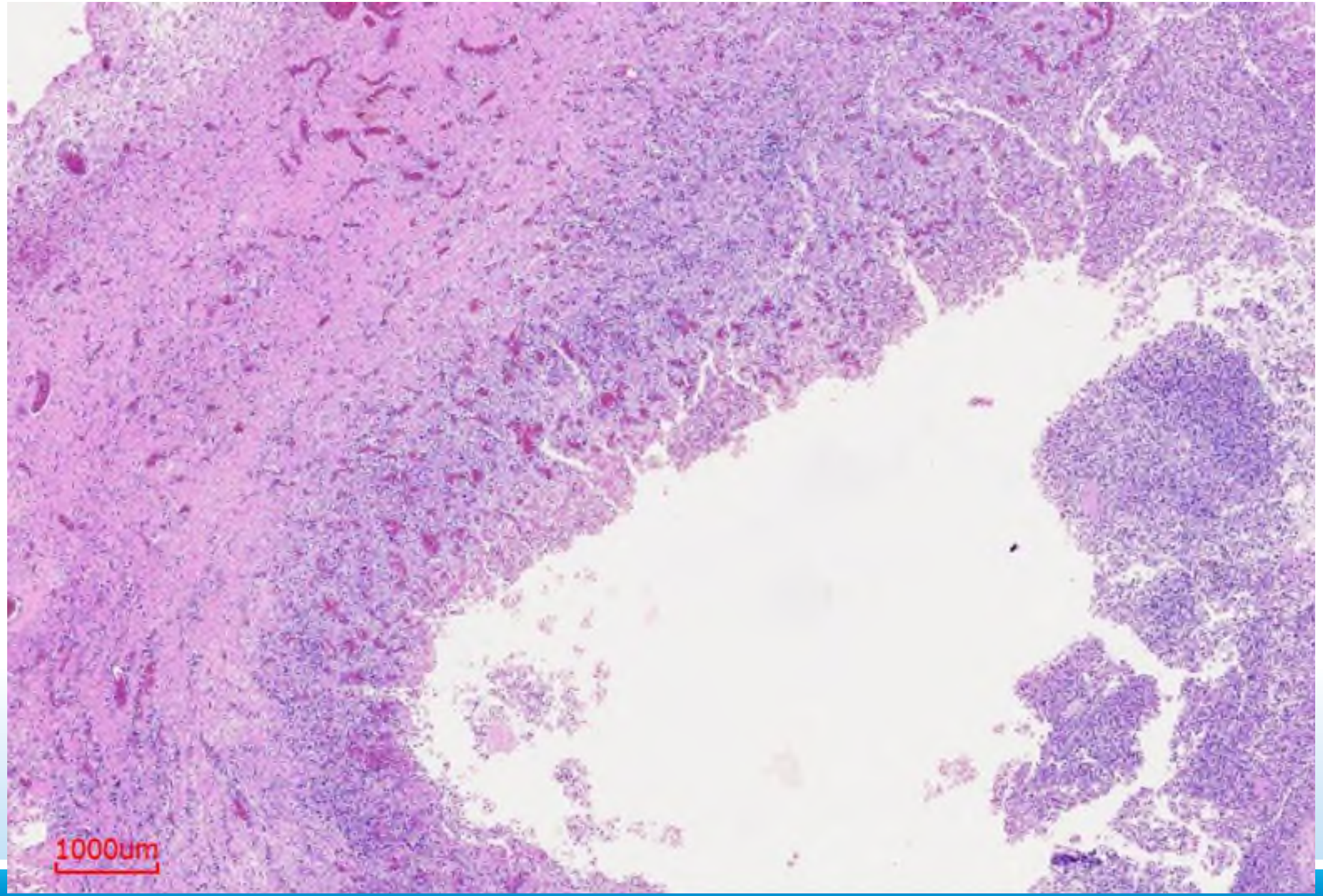


Pyogenic Abscess

Hematogenic origin

Abscesses – Surgical specimens



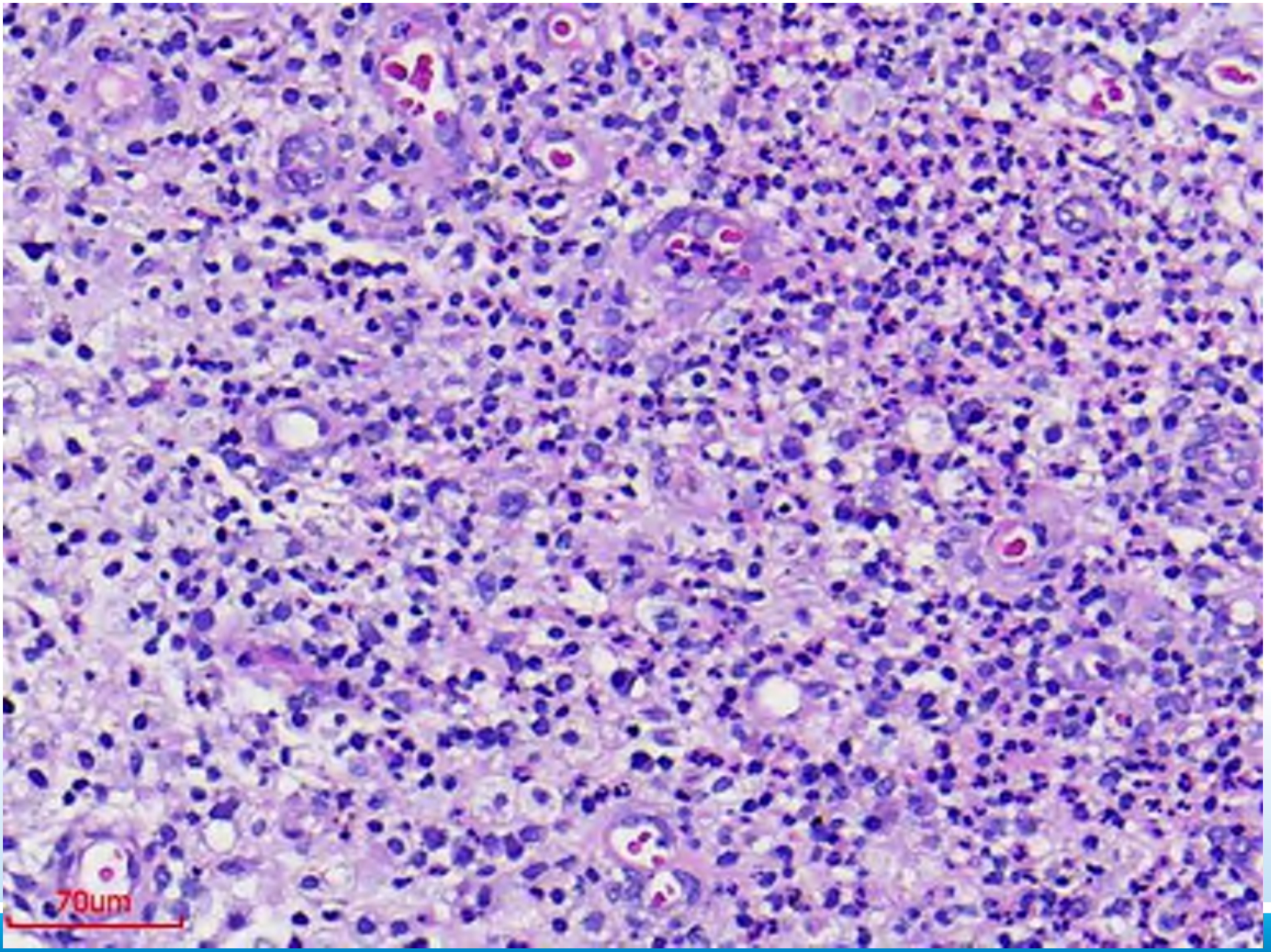


Pyogenic Abscess

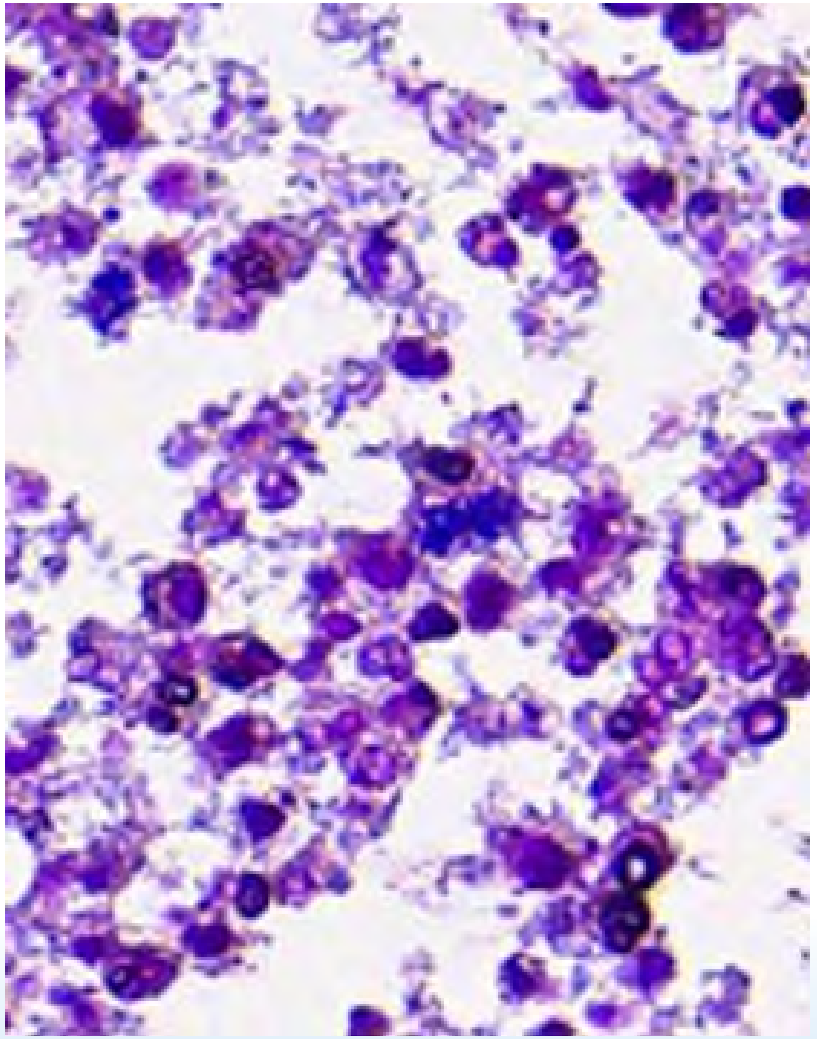
Granulation Tissue

Fibrous wall

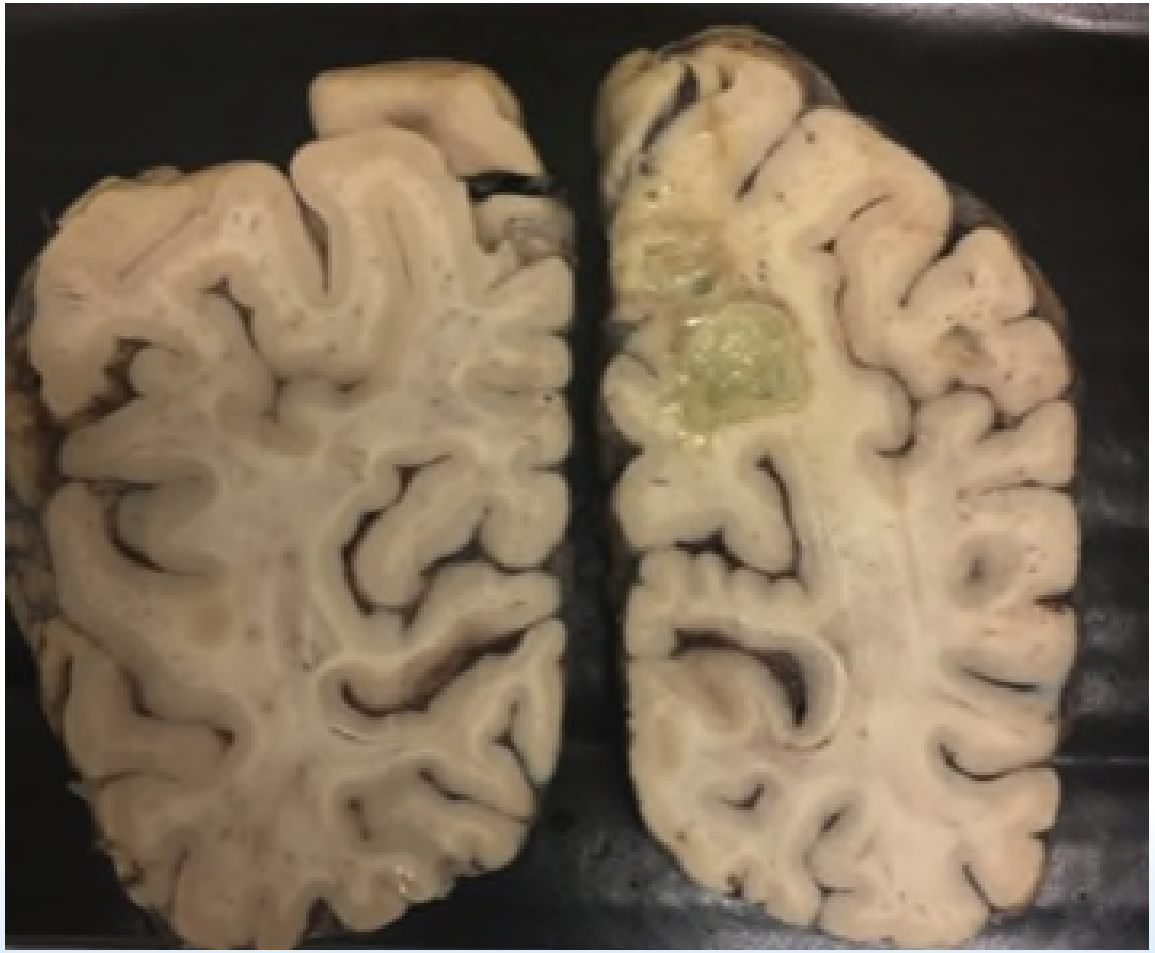
Pyogenic contents rich in PMN neutrophils

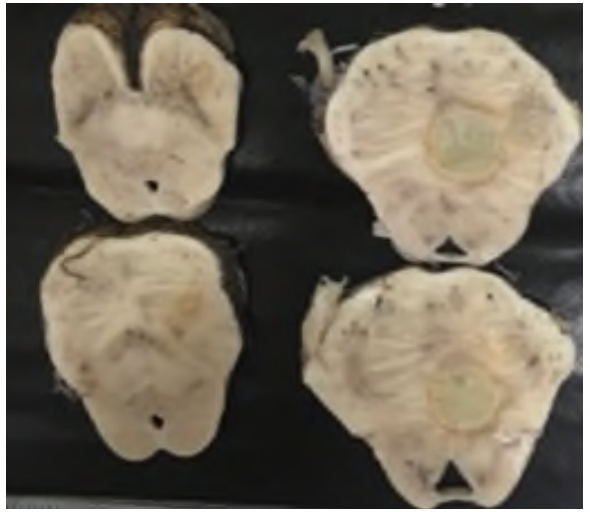


Gram + cocci

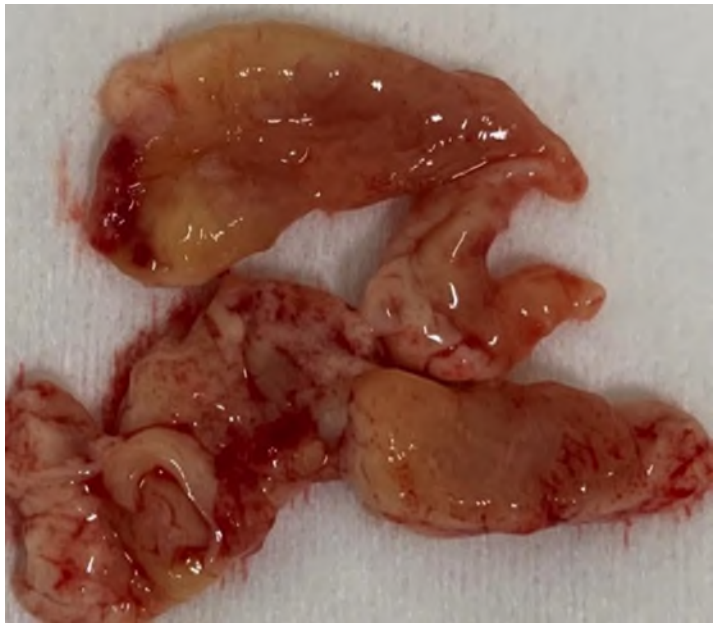


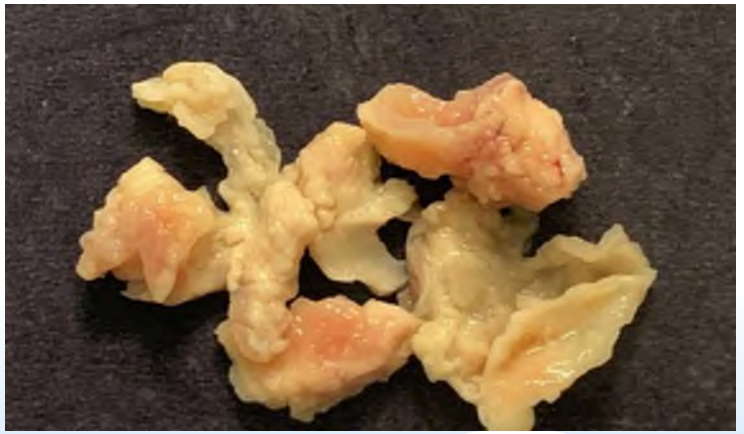
Less frequent bacterial abscess



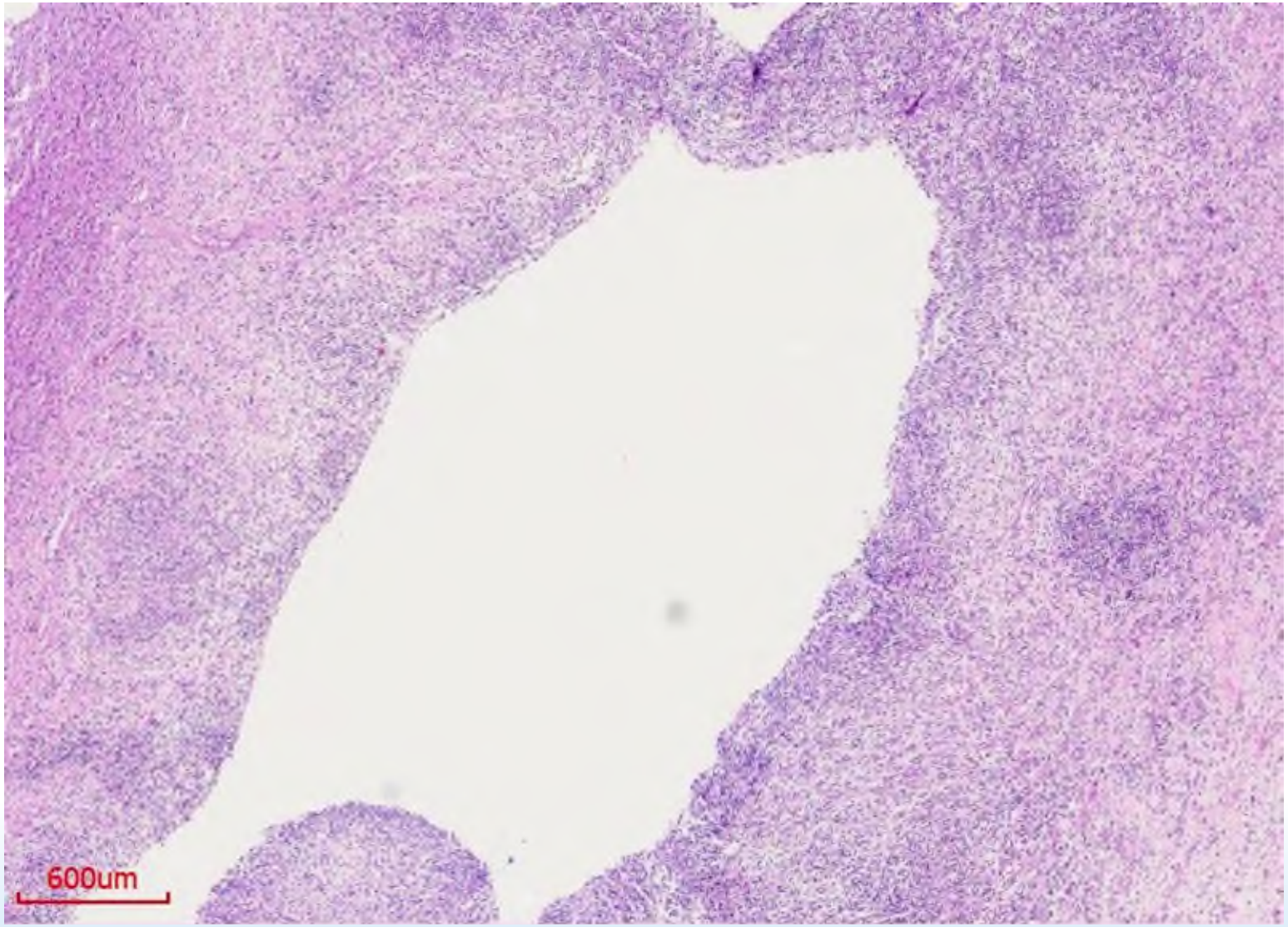


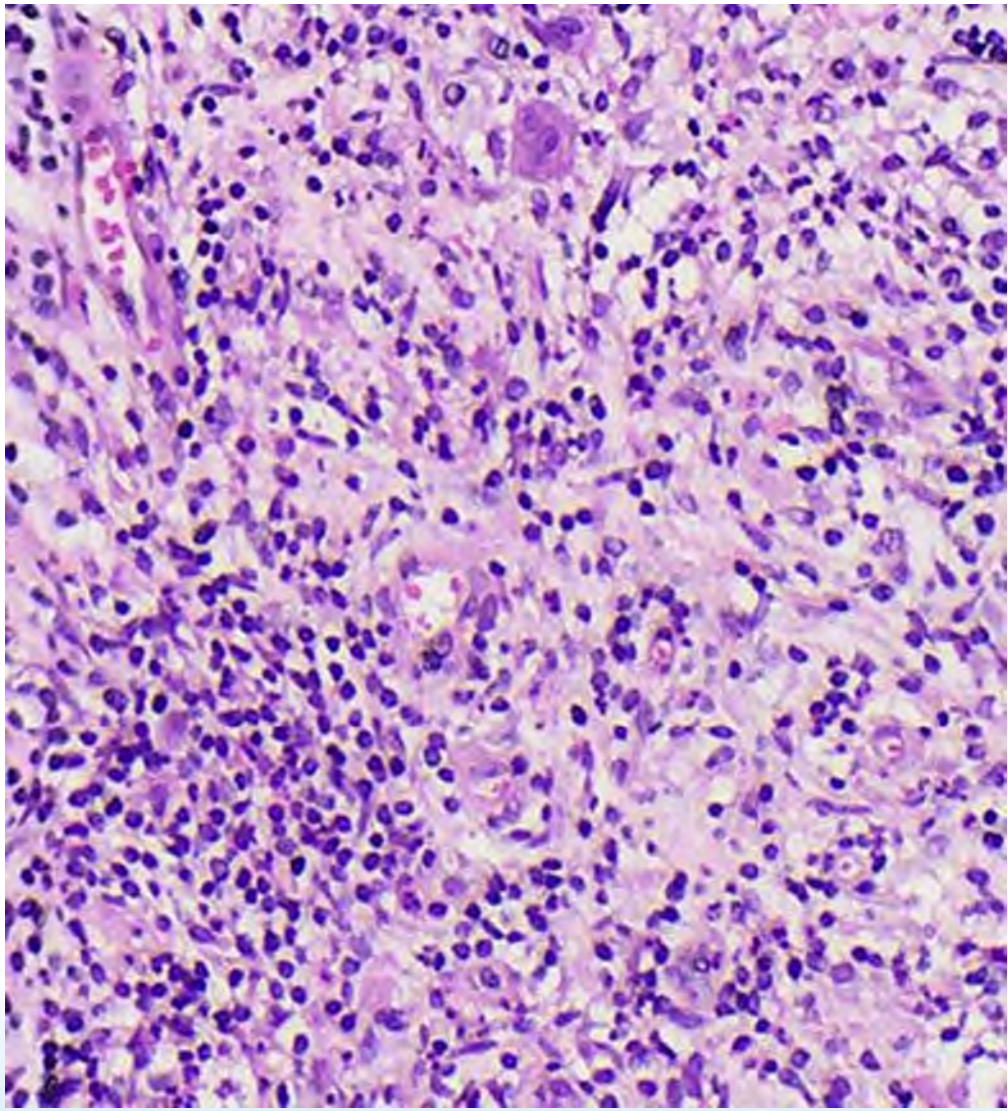
Surgical specimen



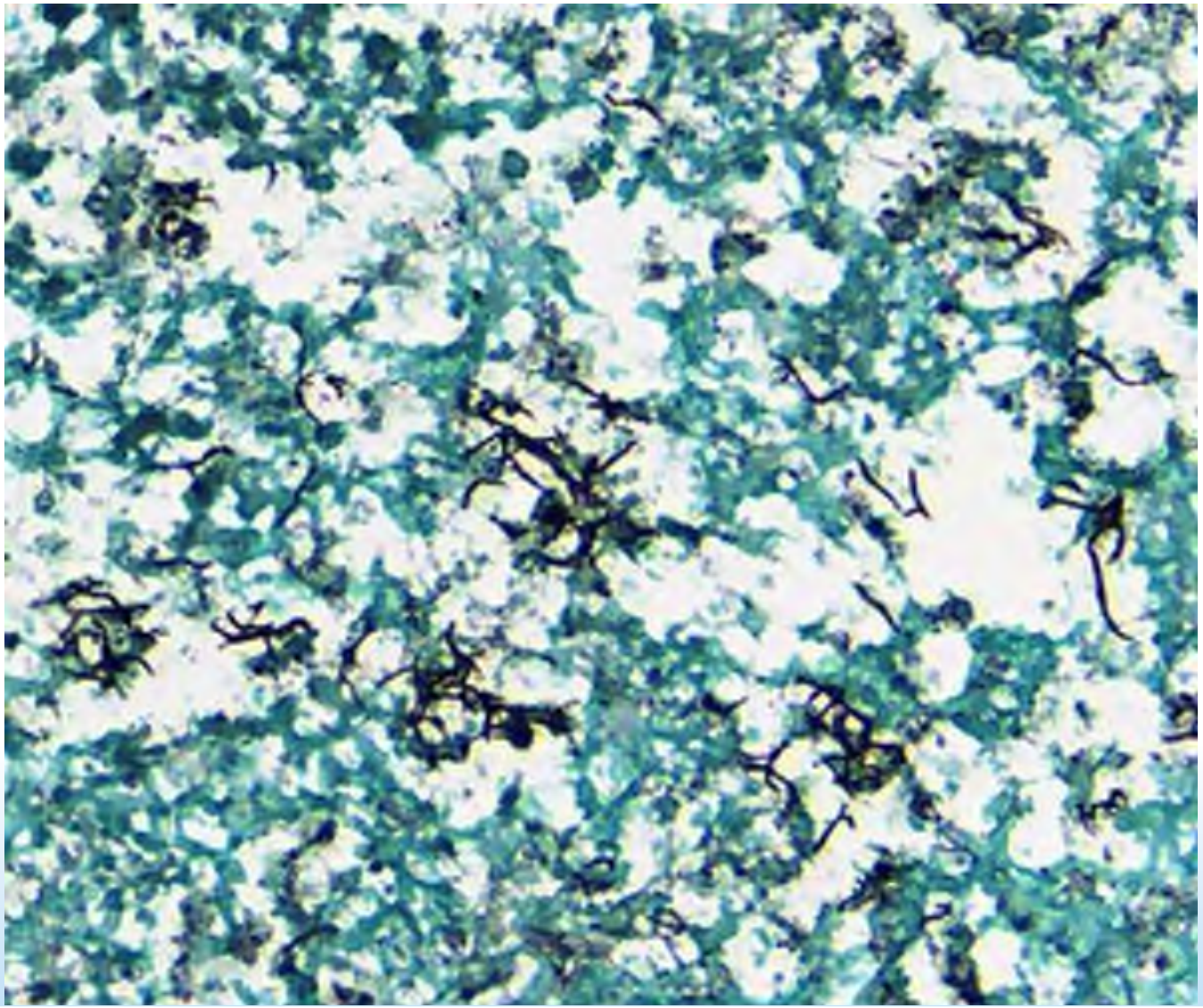


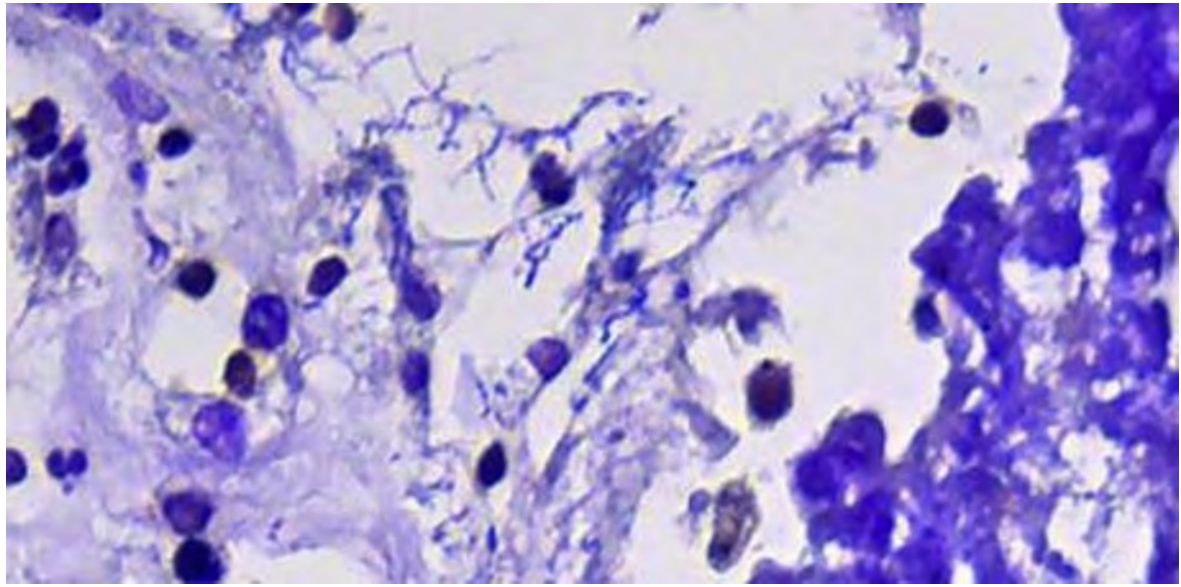
Courtesy of Dr. T Freire

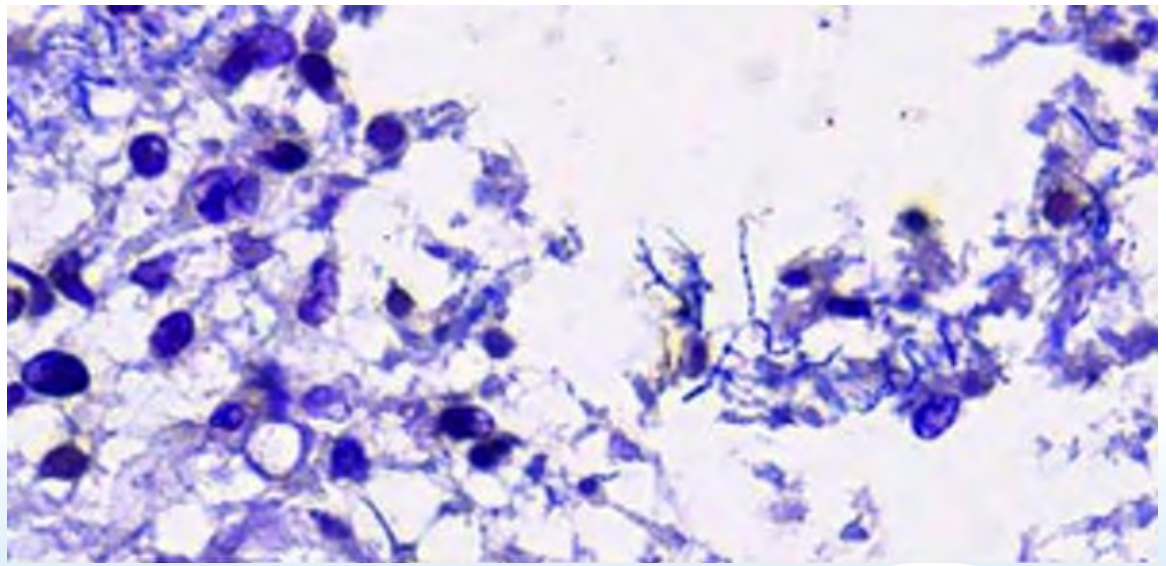

600um



Filaments Grocott and Gram (+)







Diagnosis - Nocardia

TUBERCULOSIS

- Still a major health problem
- Endemic in developing countries with a large population, crowding and poverty
- Cerebral Tuberculosis
    - Tuberculous meningitis
    - Tuberculoma
    - Tuberculous abscess

Tuberculous Meningitis

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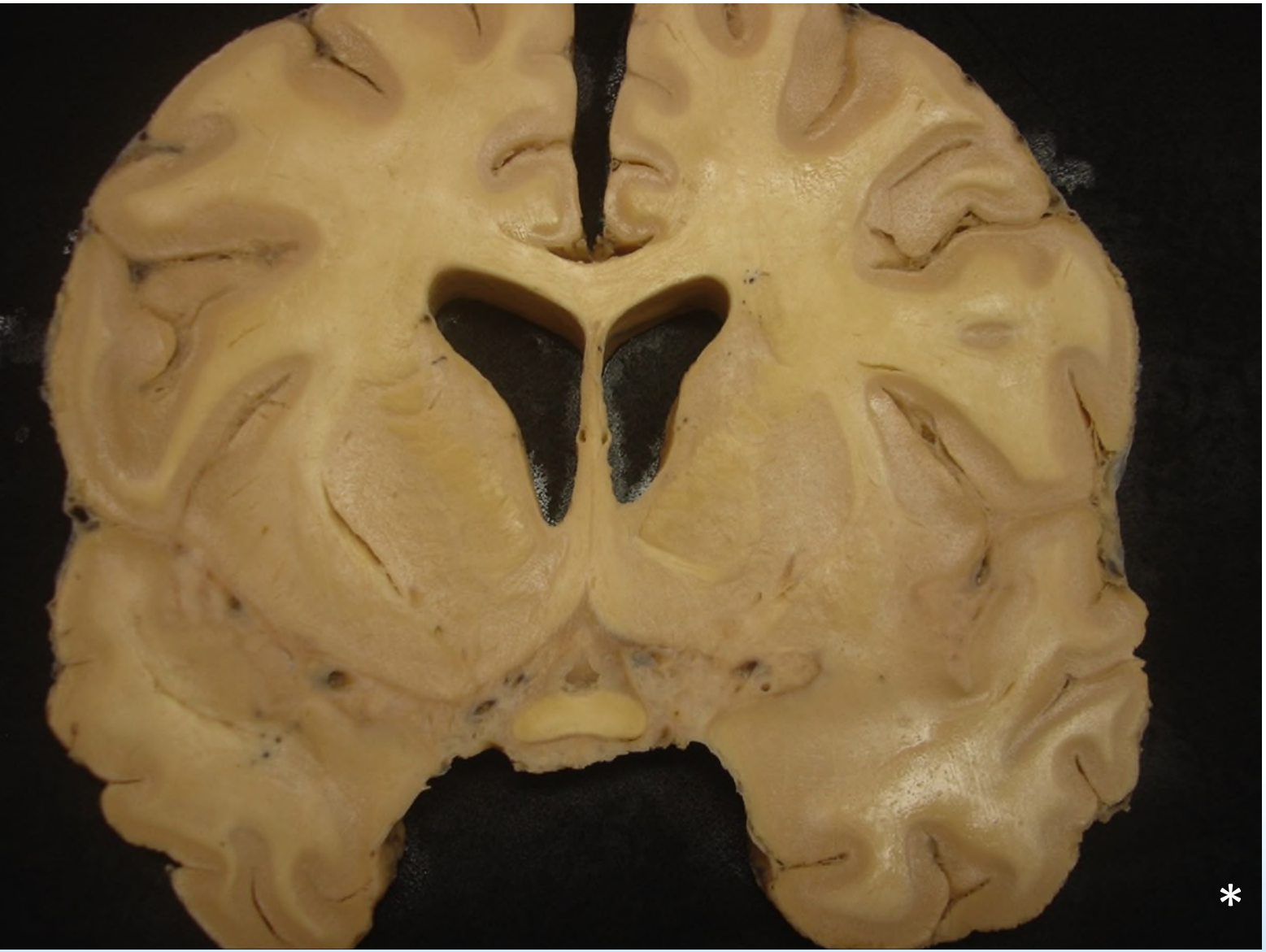
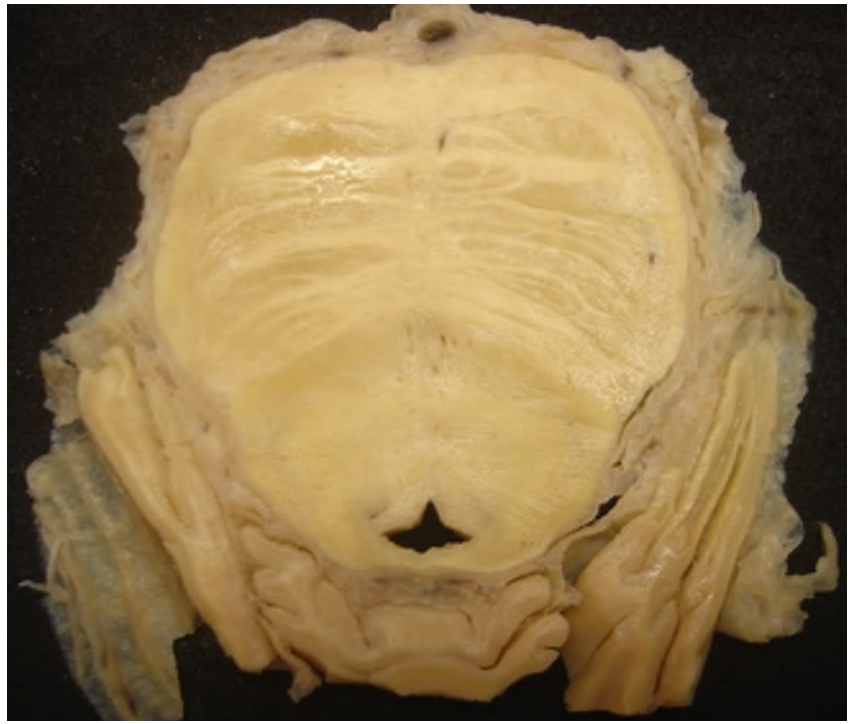
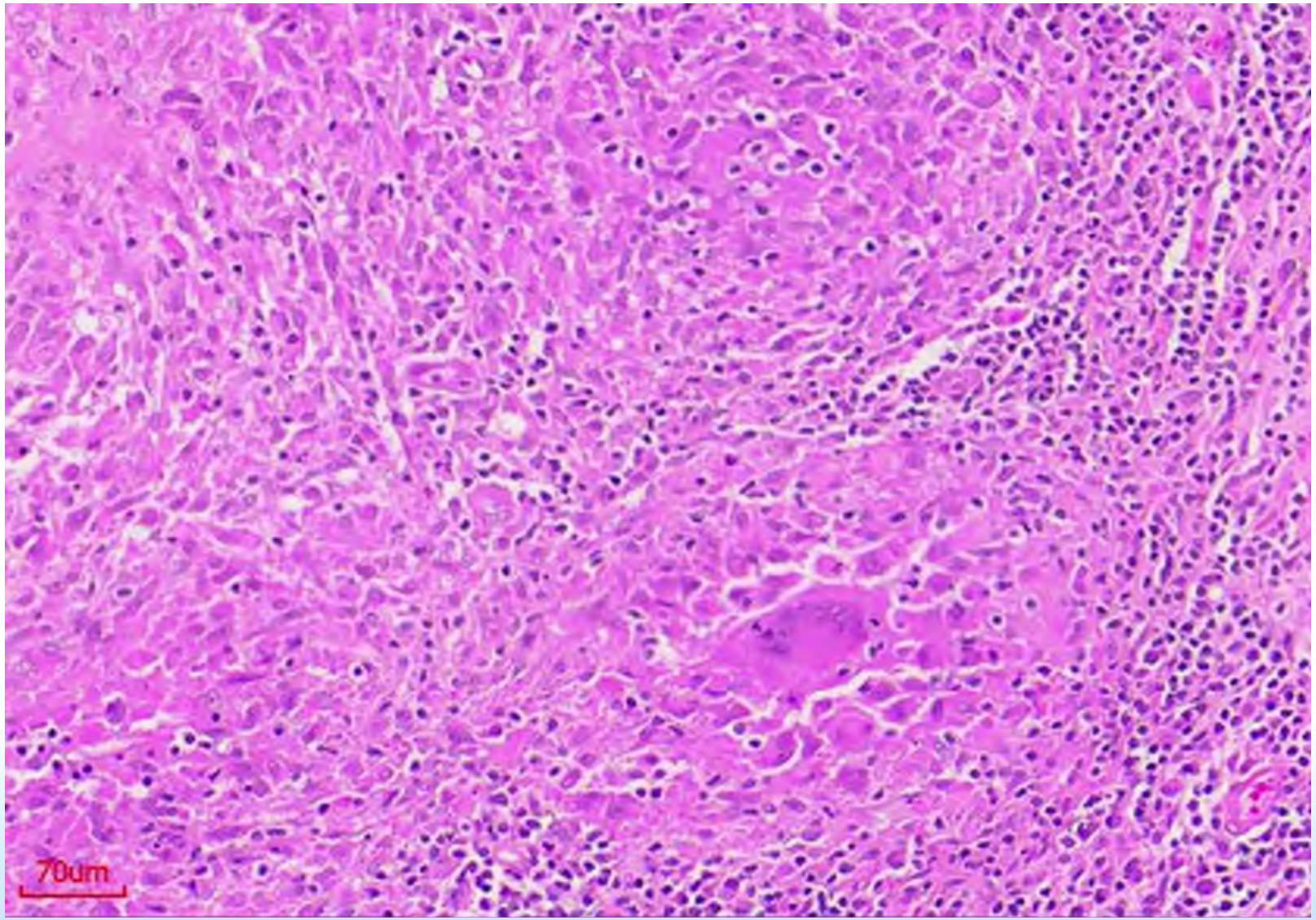
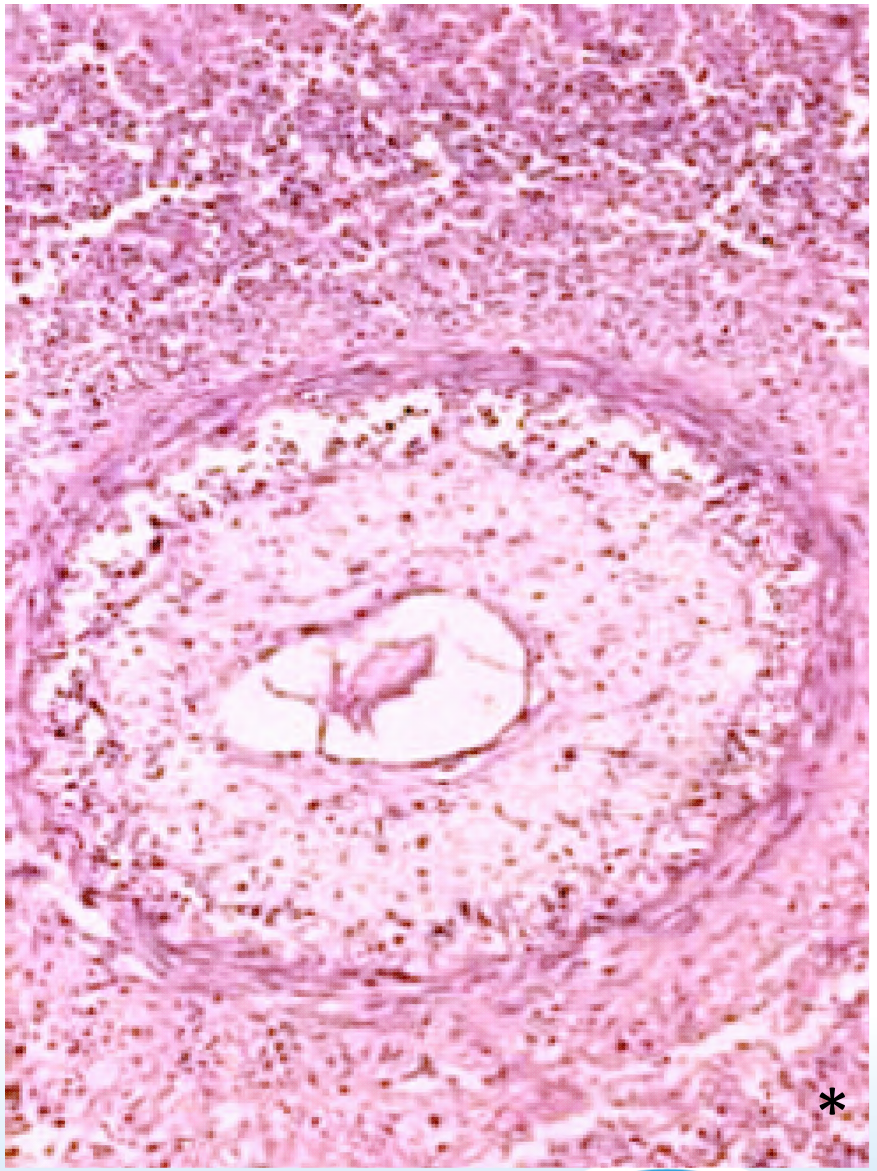


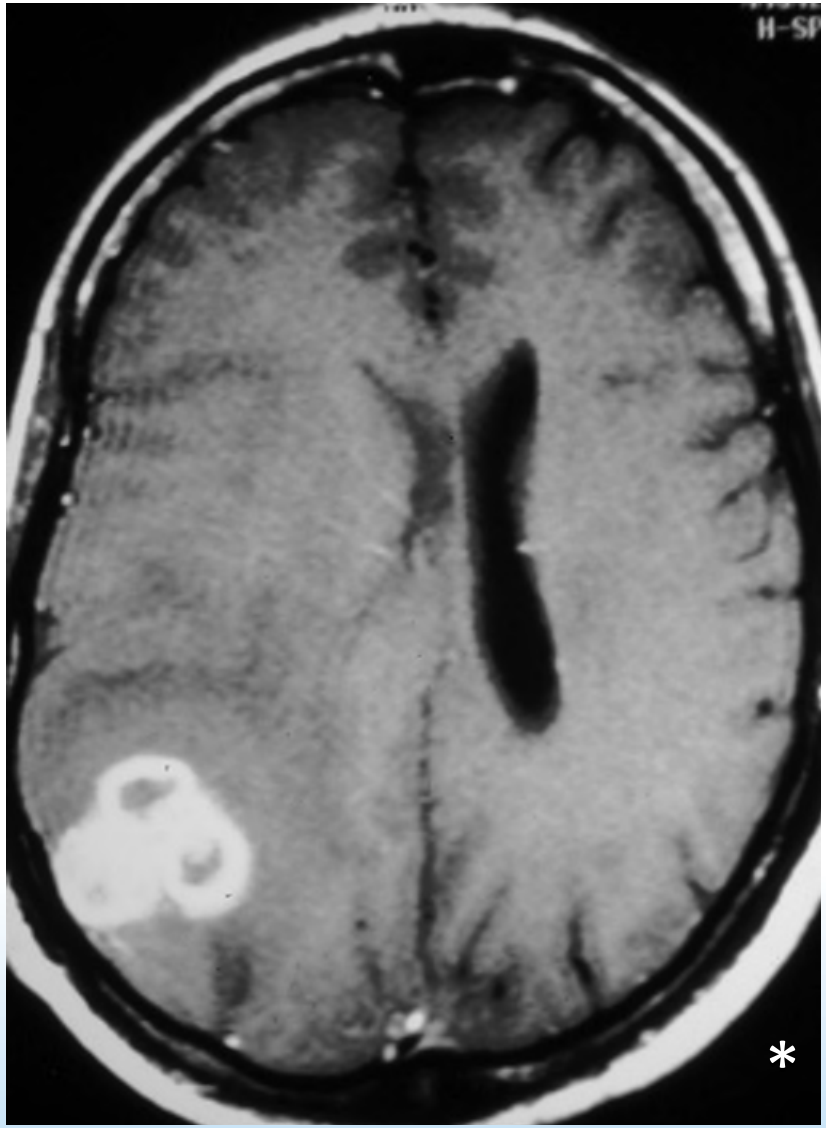


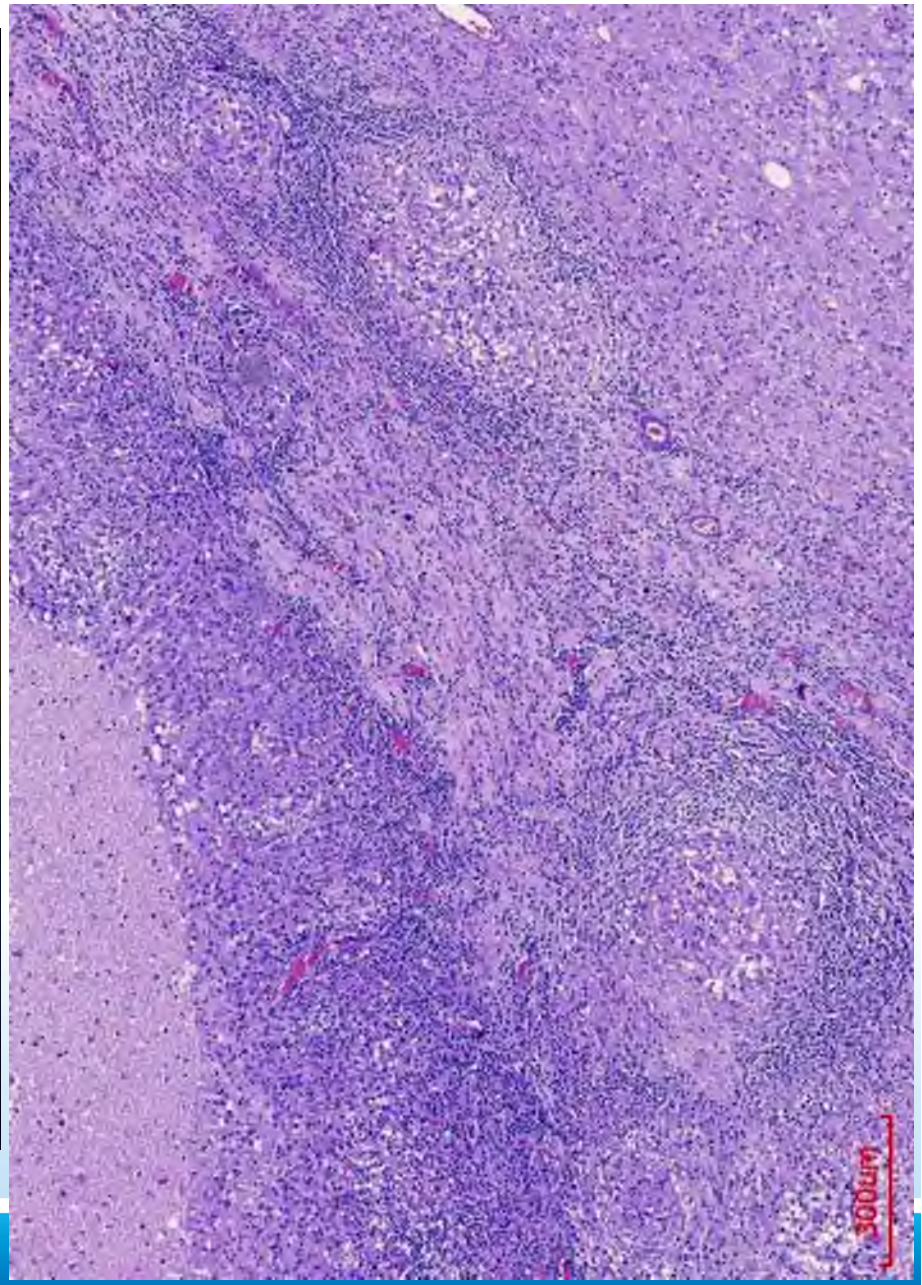
Granuloma and vasculitis (infarct)

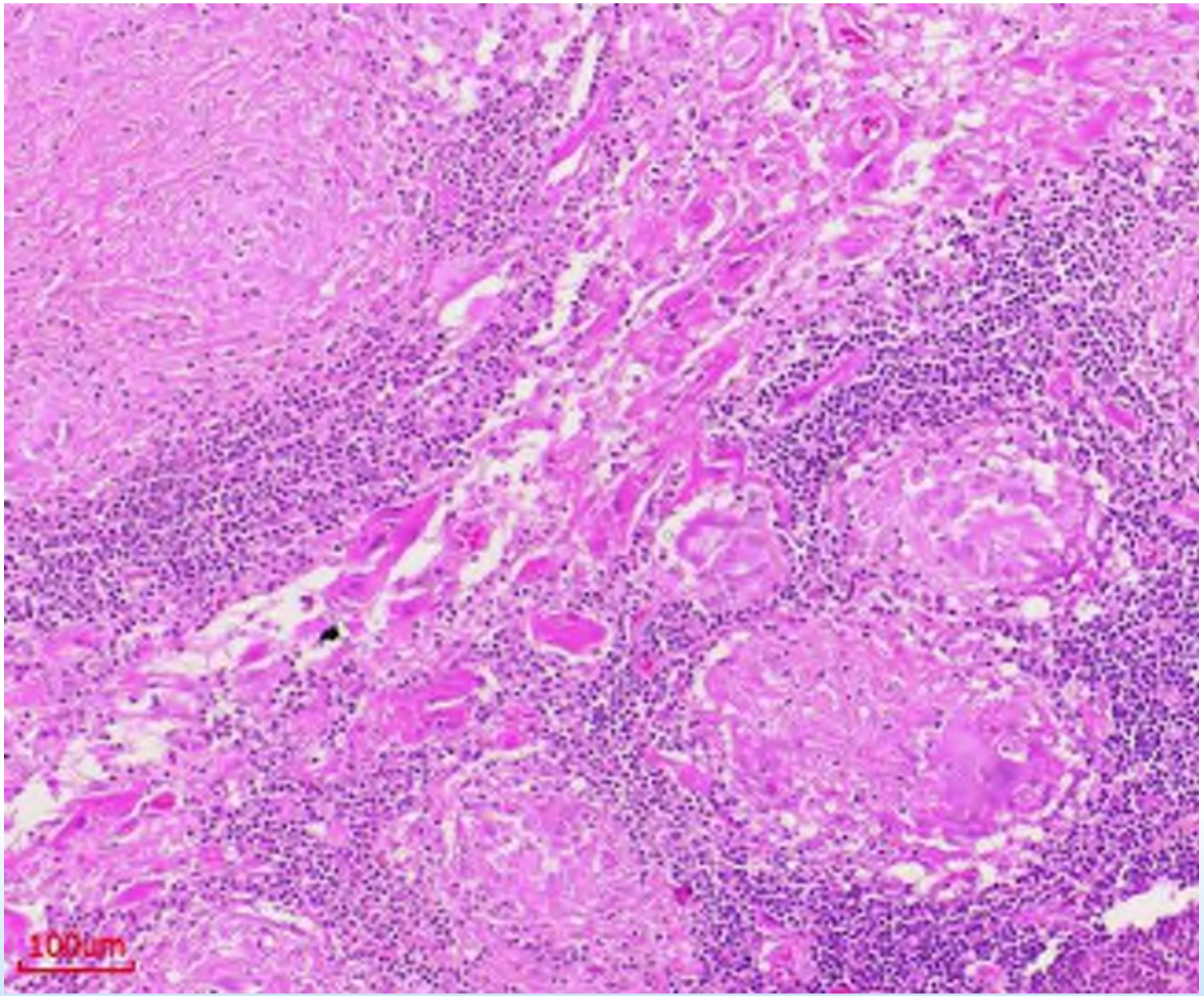


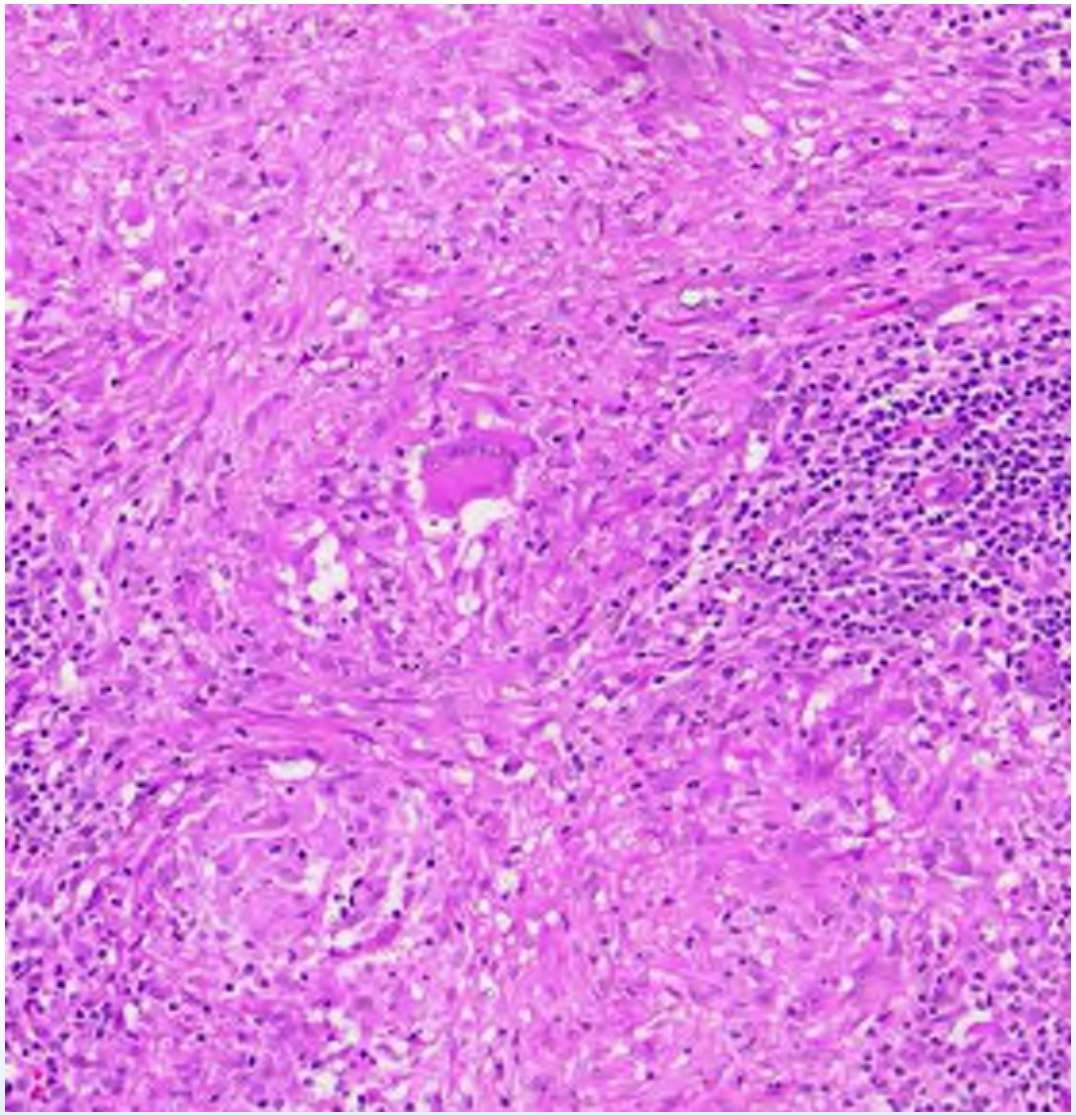


Tuberculoma

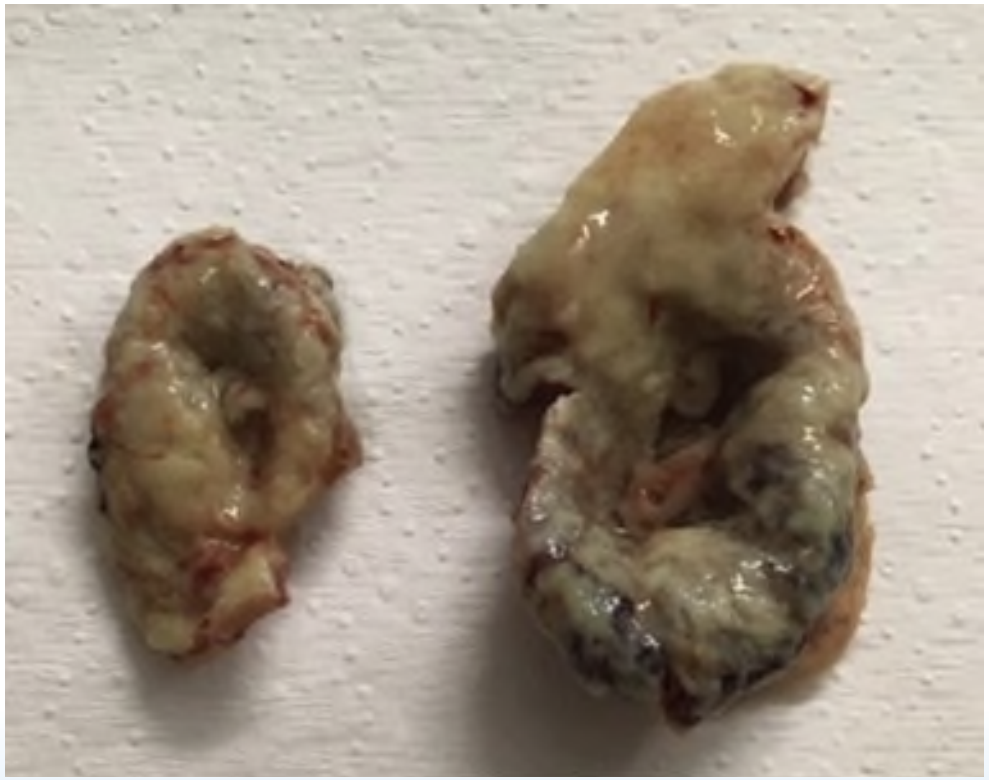


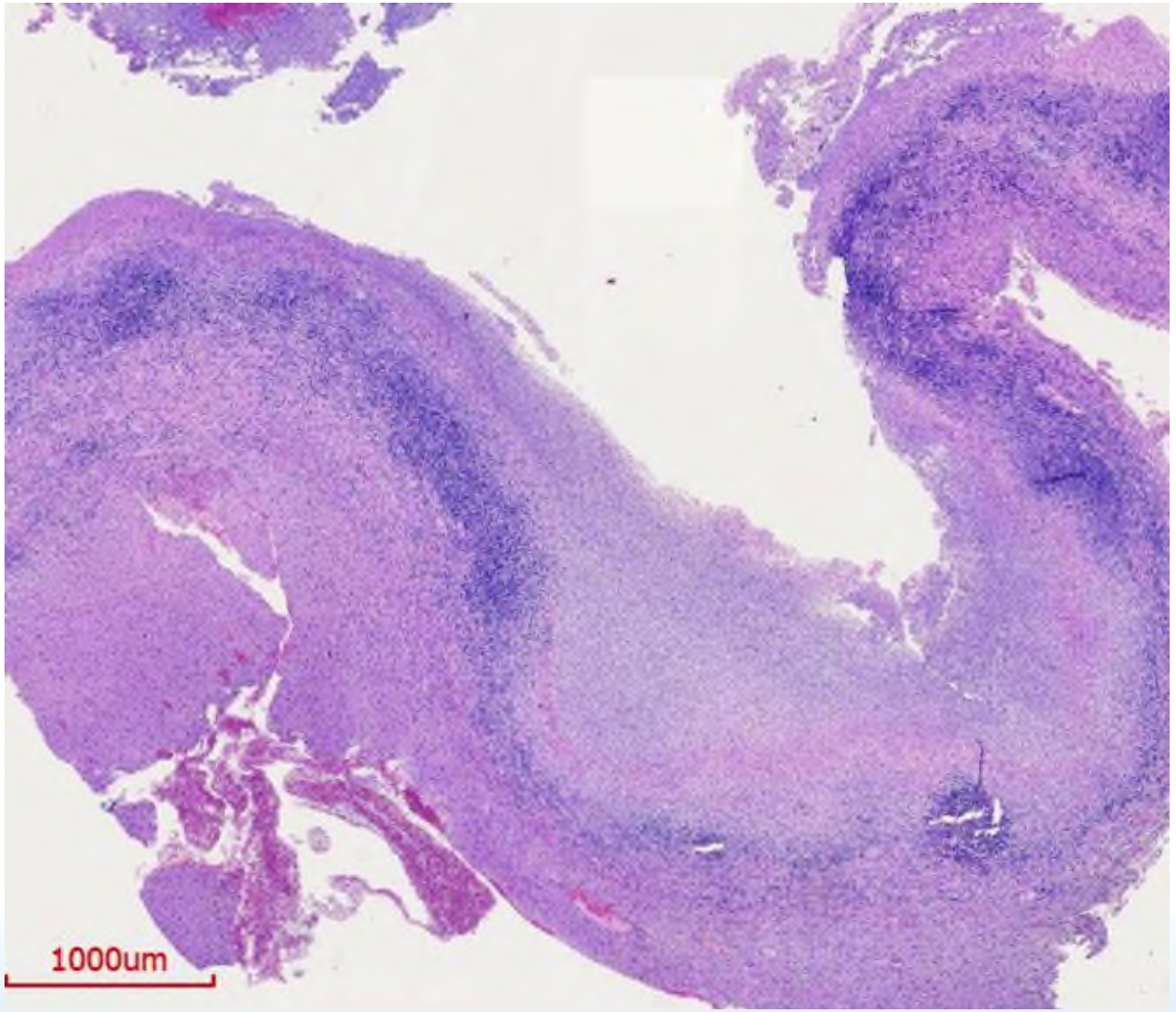



100um

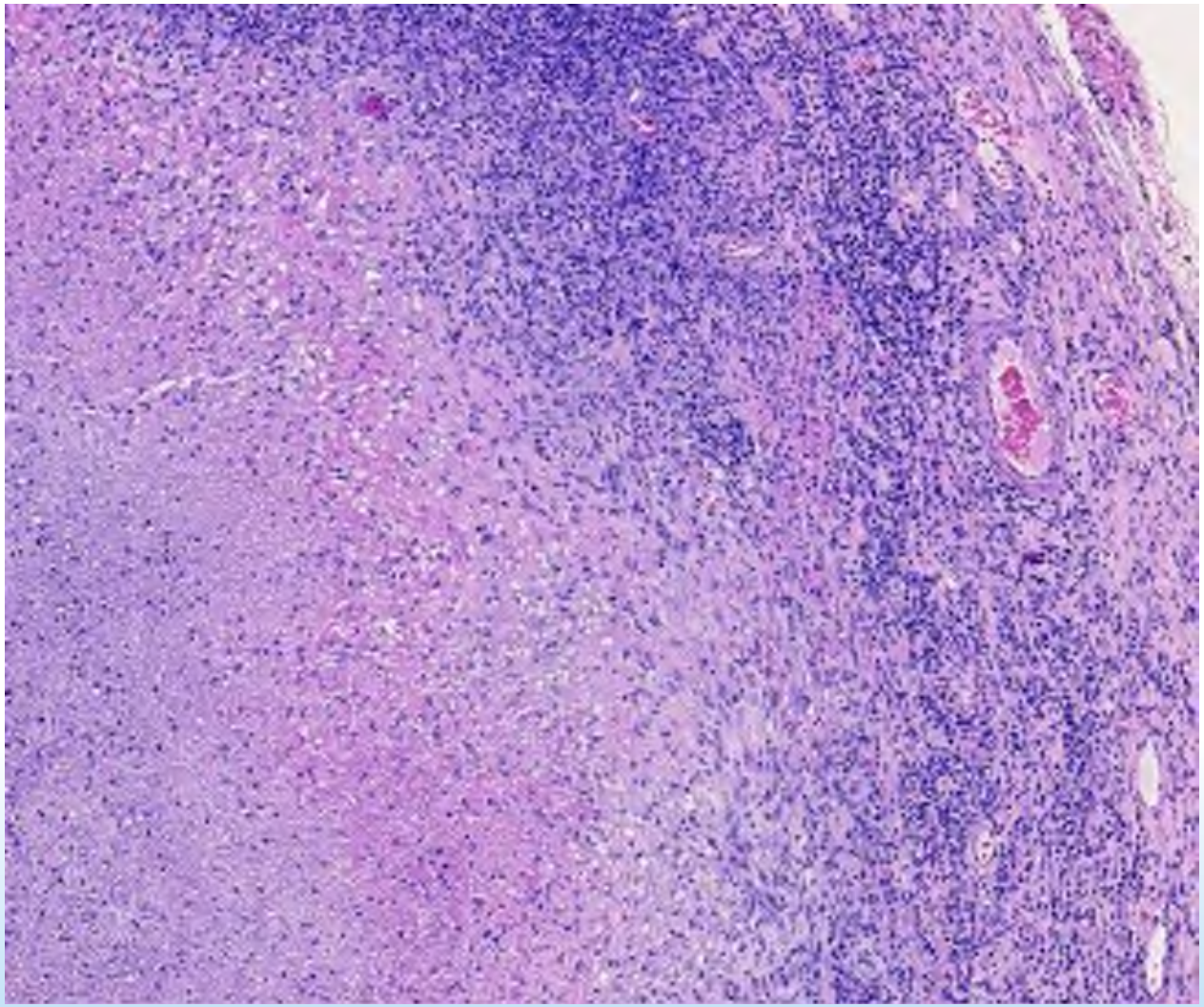


Abscess in an immunodeficient young male

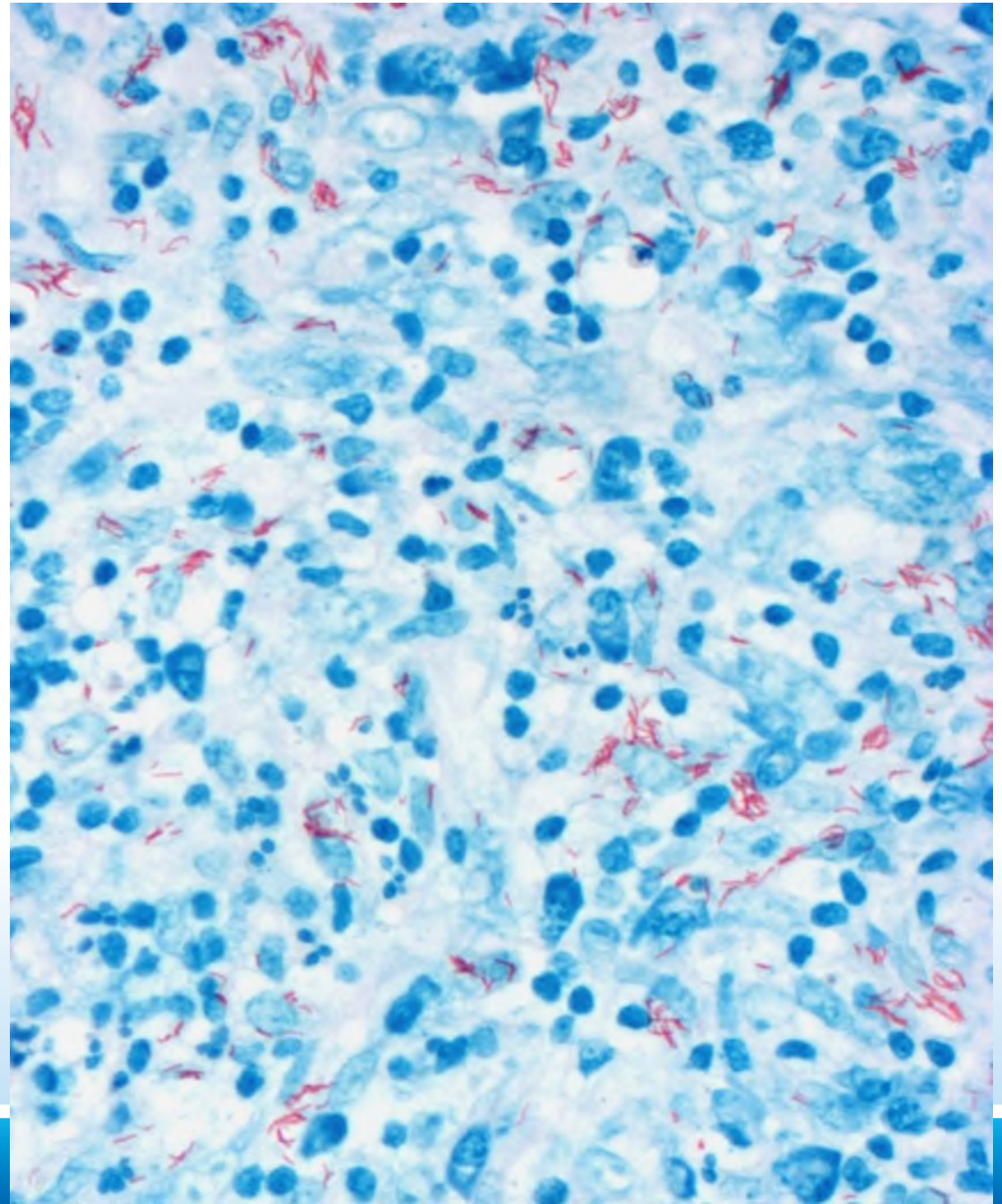


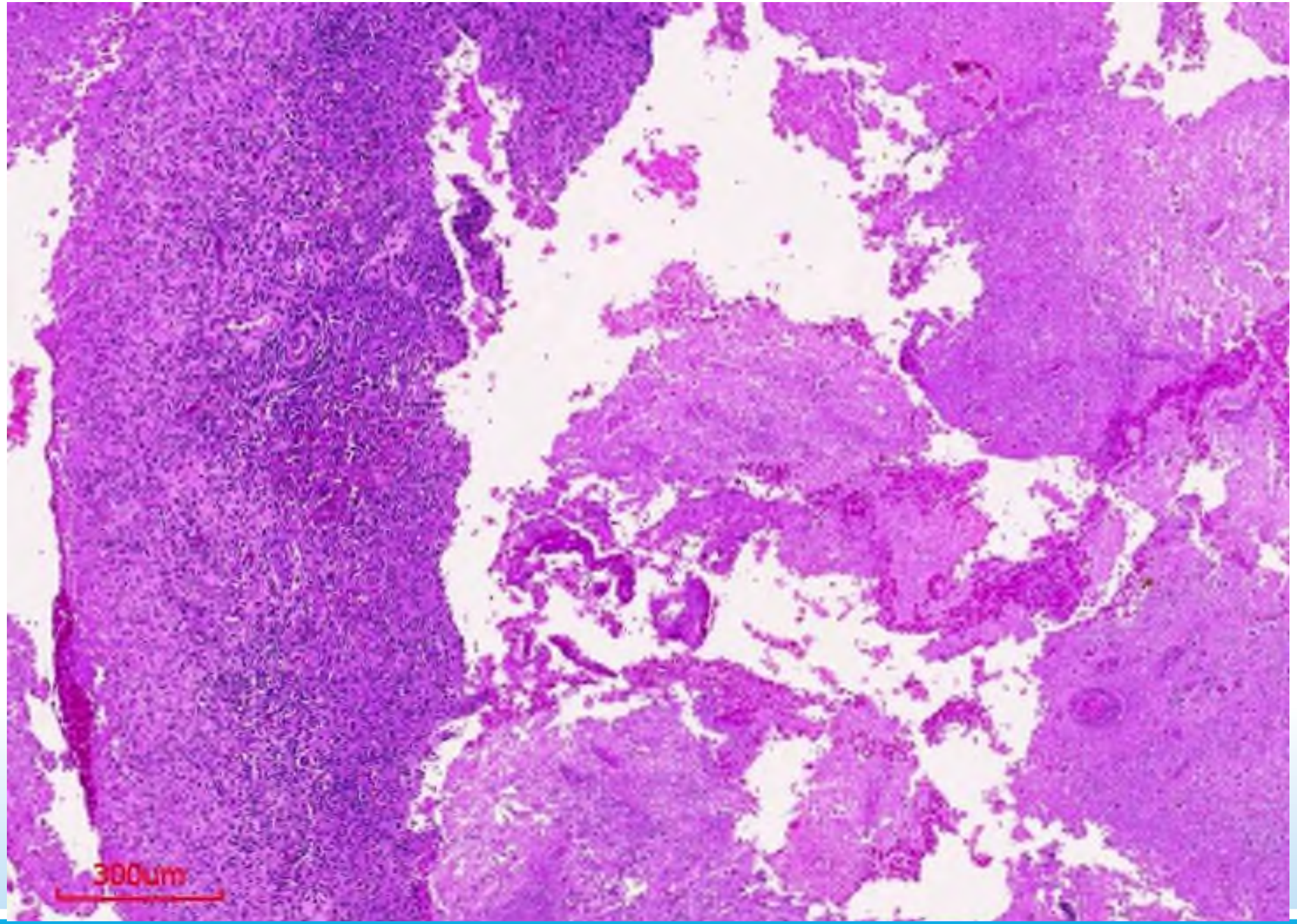


Tuberculous Abscess



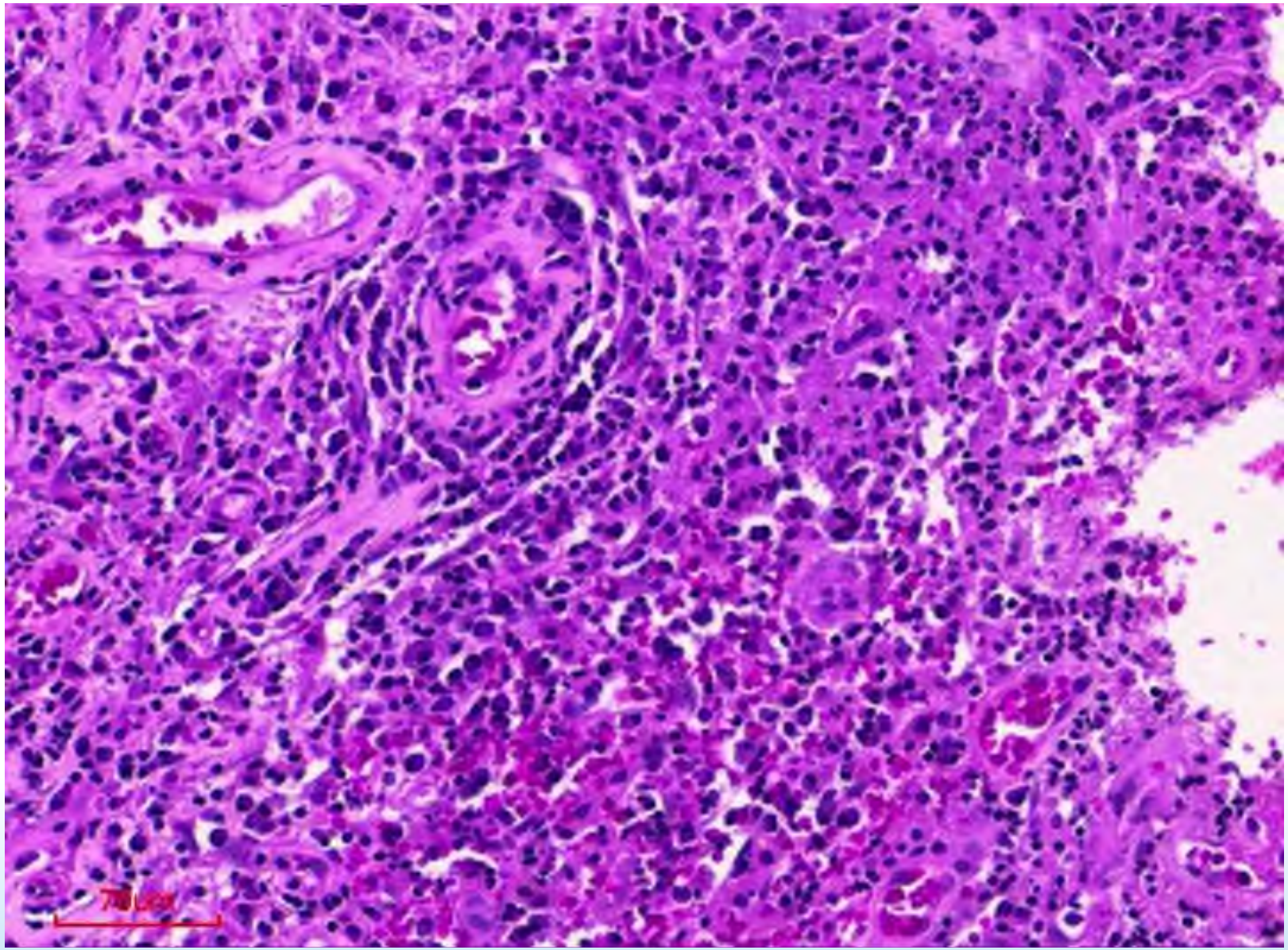
Ziehl Nielsen staining shows numerous acid fast bacilli

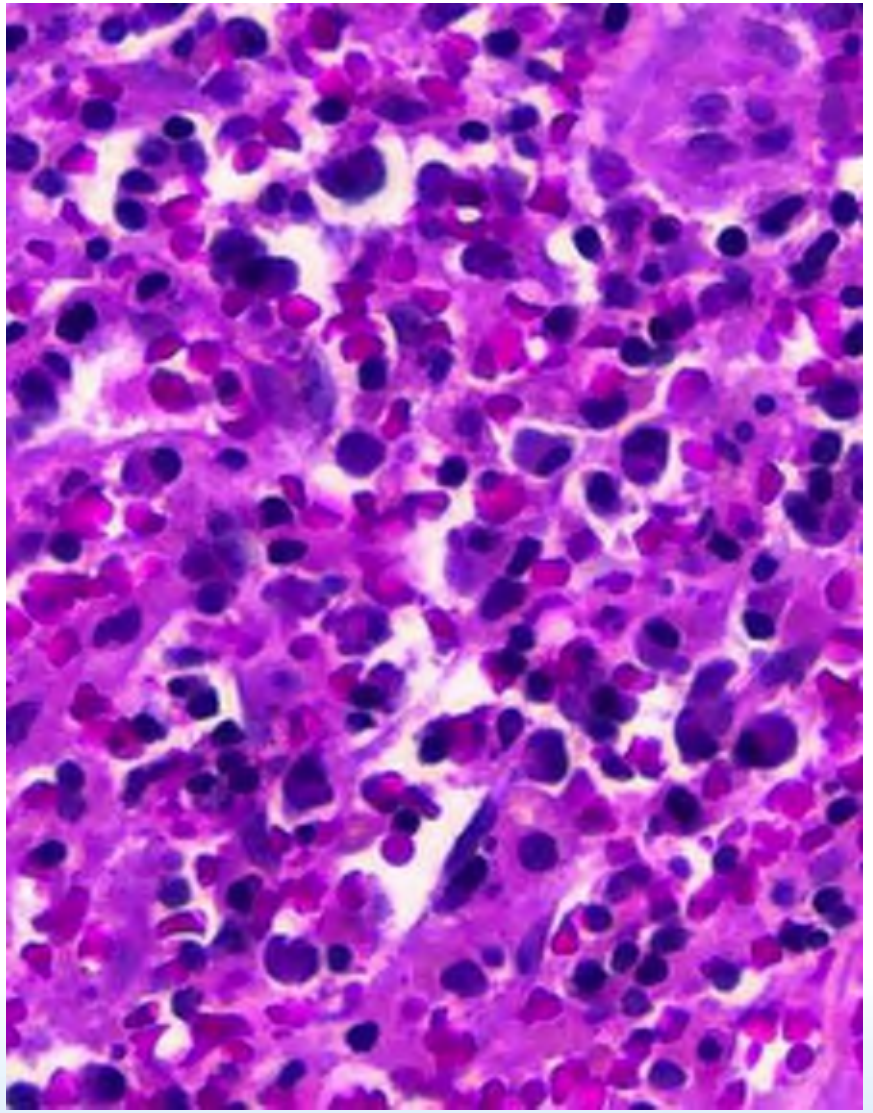




Syphilis

Meningovascular
Goma
Tabes dorsalis





Etiology

Bacterial: Pyogenic (Gram + / -), Tuberculosis, Syphilis

Fungal: Cryptococcosis, Histoplasmosis, Mucormycosis, Aspergillosis, Paracoccidioidomycosis.

Parasitic: Protozoa: Toxoplasmosis, Amebiasis, Malaria, Trypanosomiases

Helminths: Cestodes: Cysticercosis, Hydatidosis

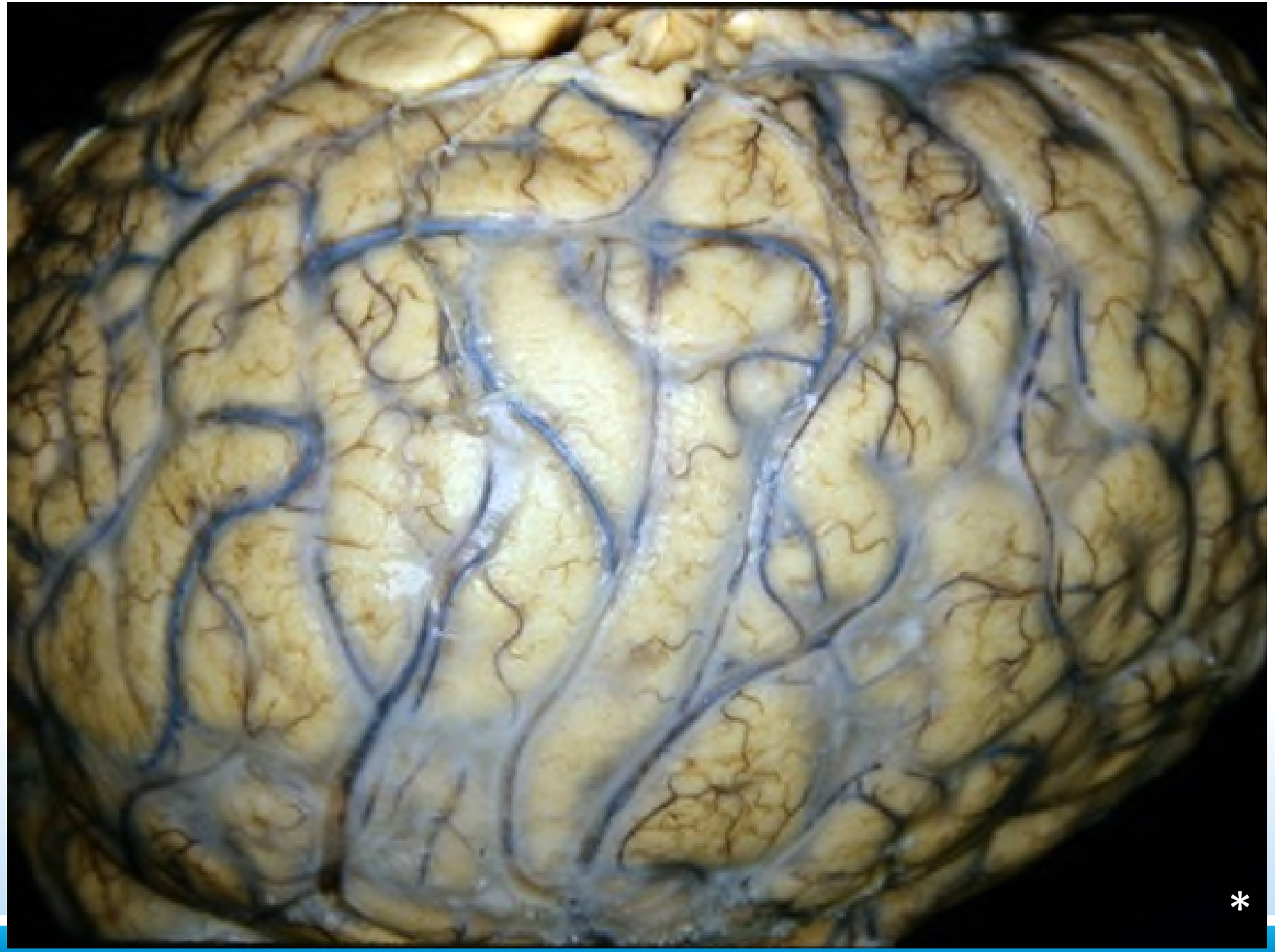
Nematodes: Strongyloidiasis

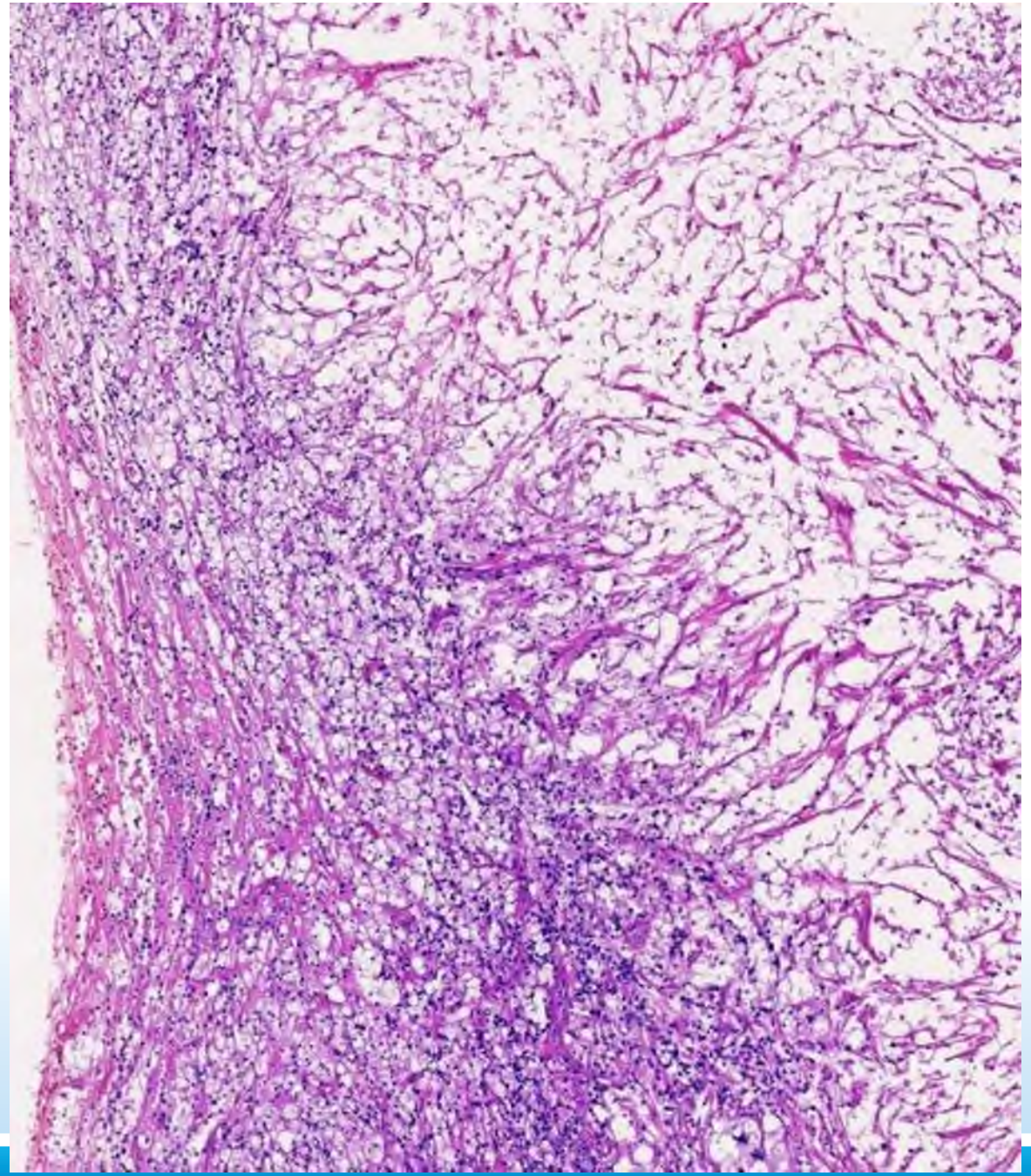
Trematodes: Schistosomiasis

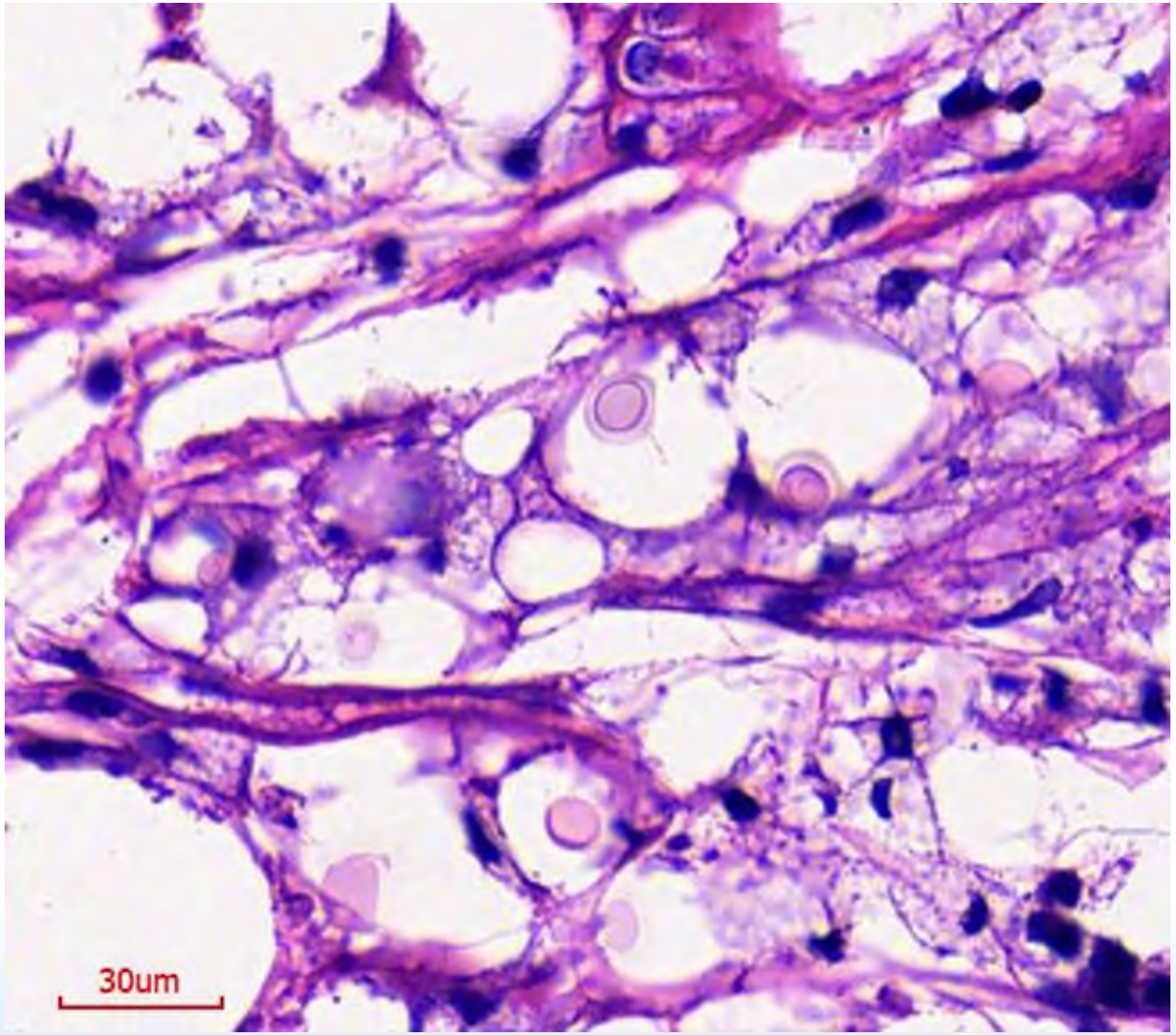
Viral: Arboviroses (Dengue, Zika), CMV, HIV, Herpes, HTLV1, Measles, Poliomyelitis, PML, Rabies.

Cryptococcosis

Meningitis
(Immunodeficient)



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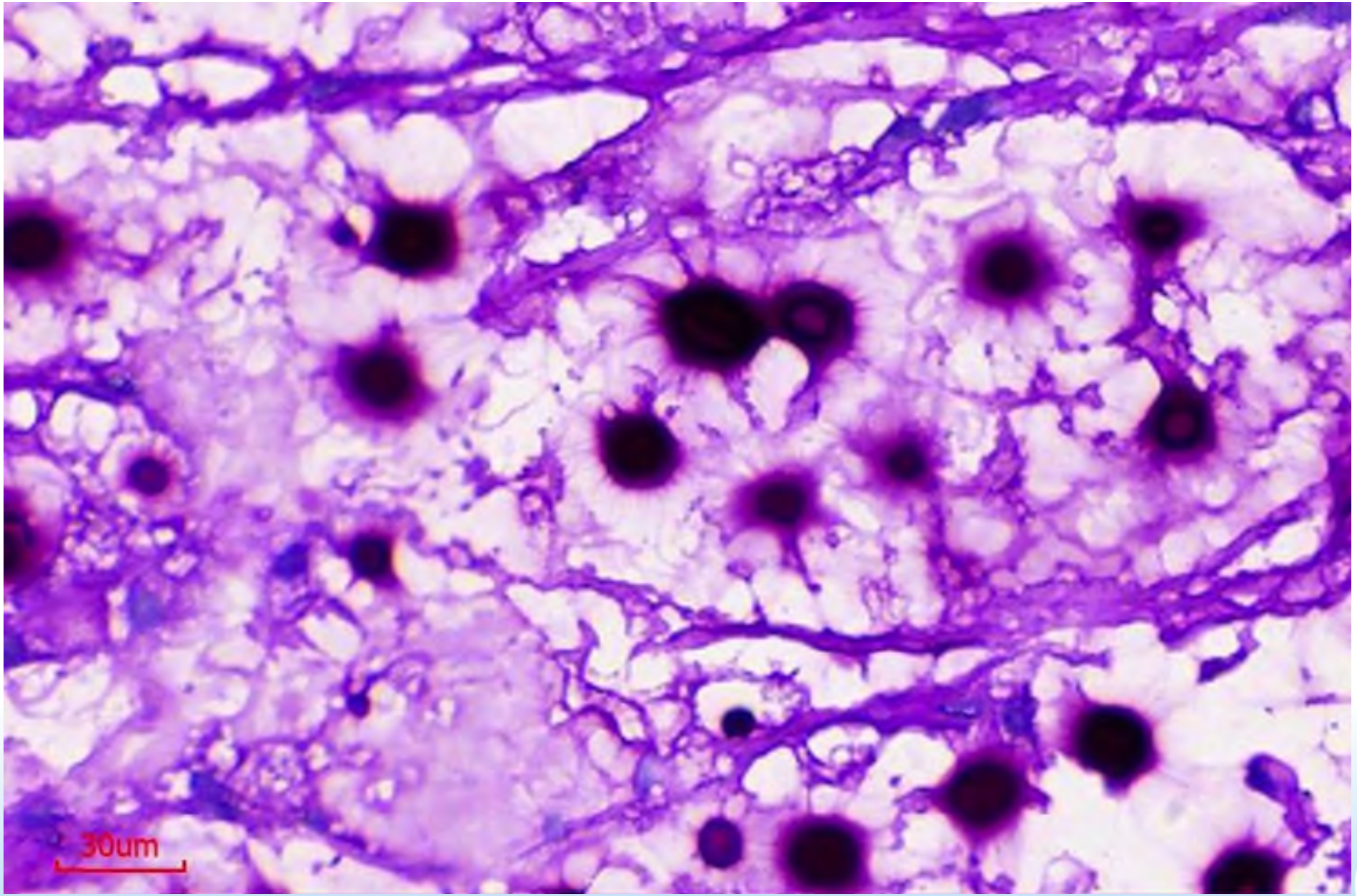
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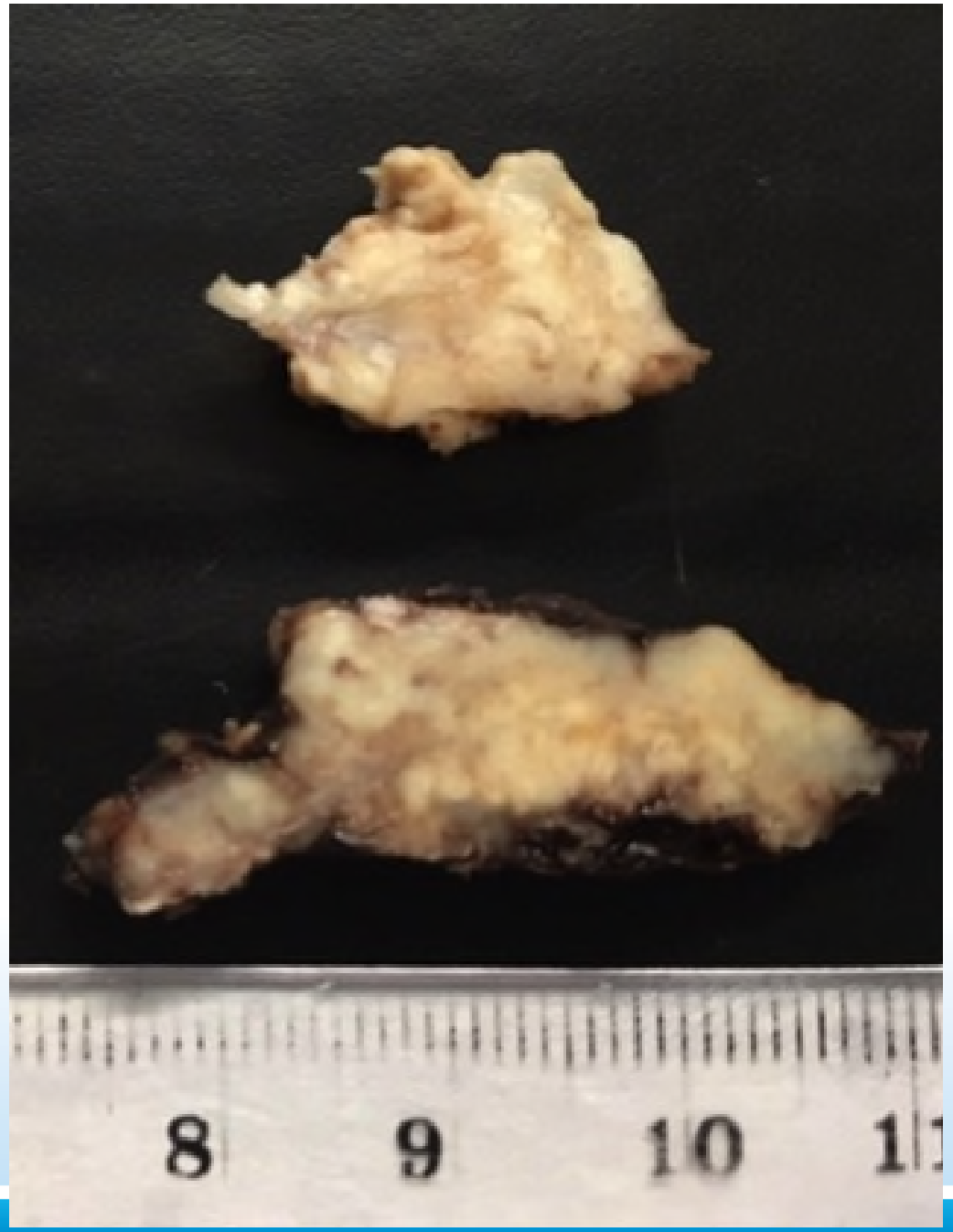
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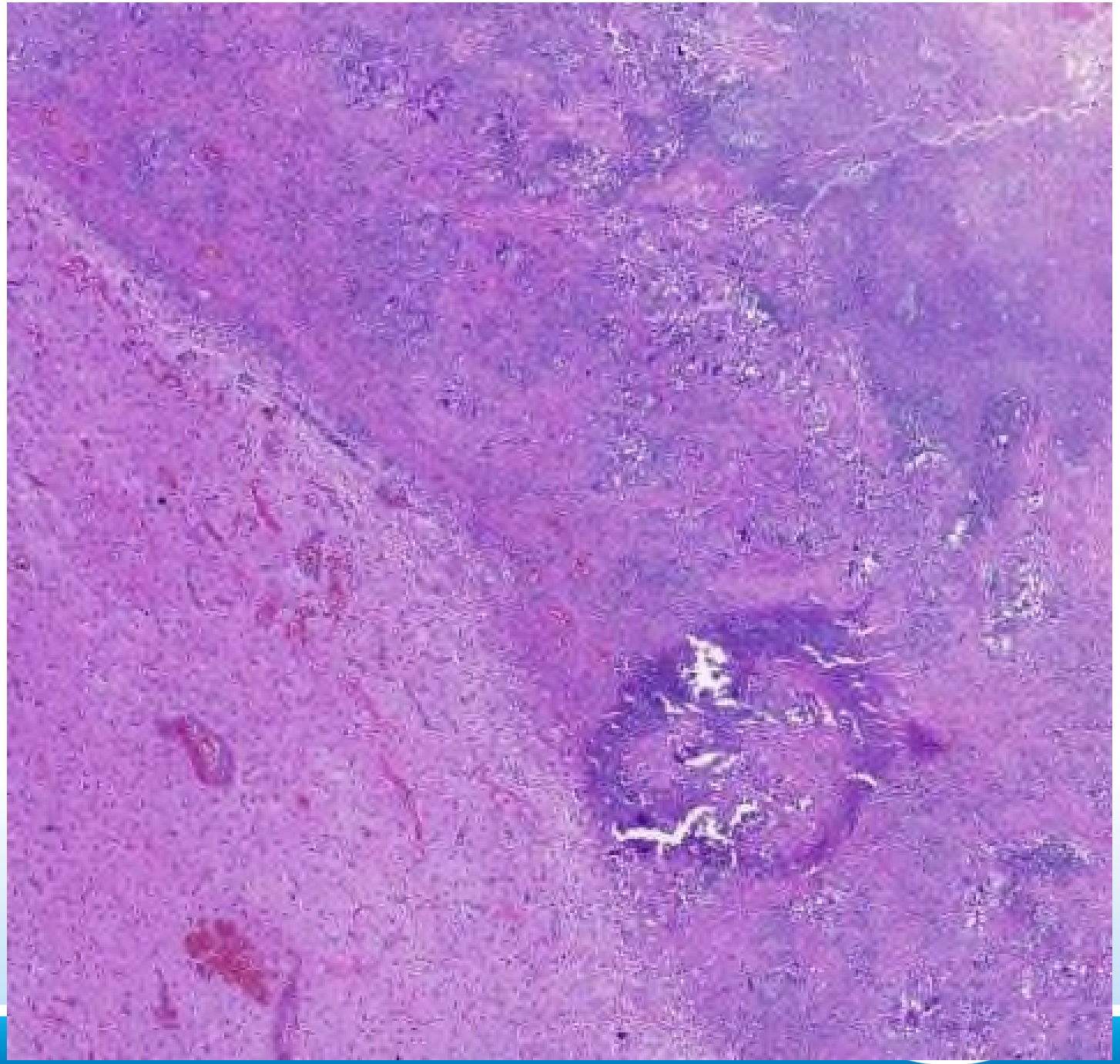

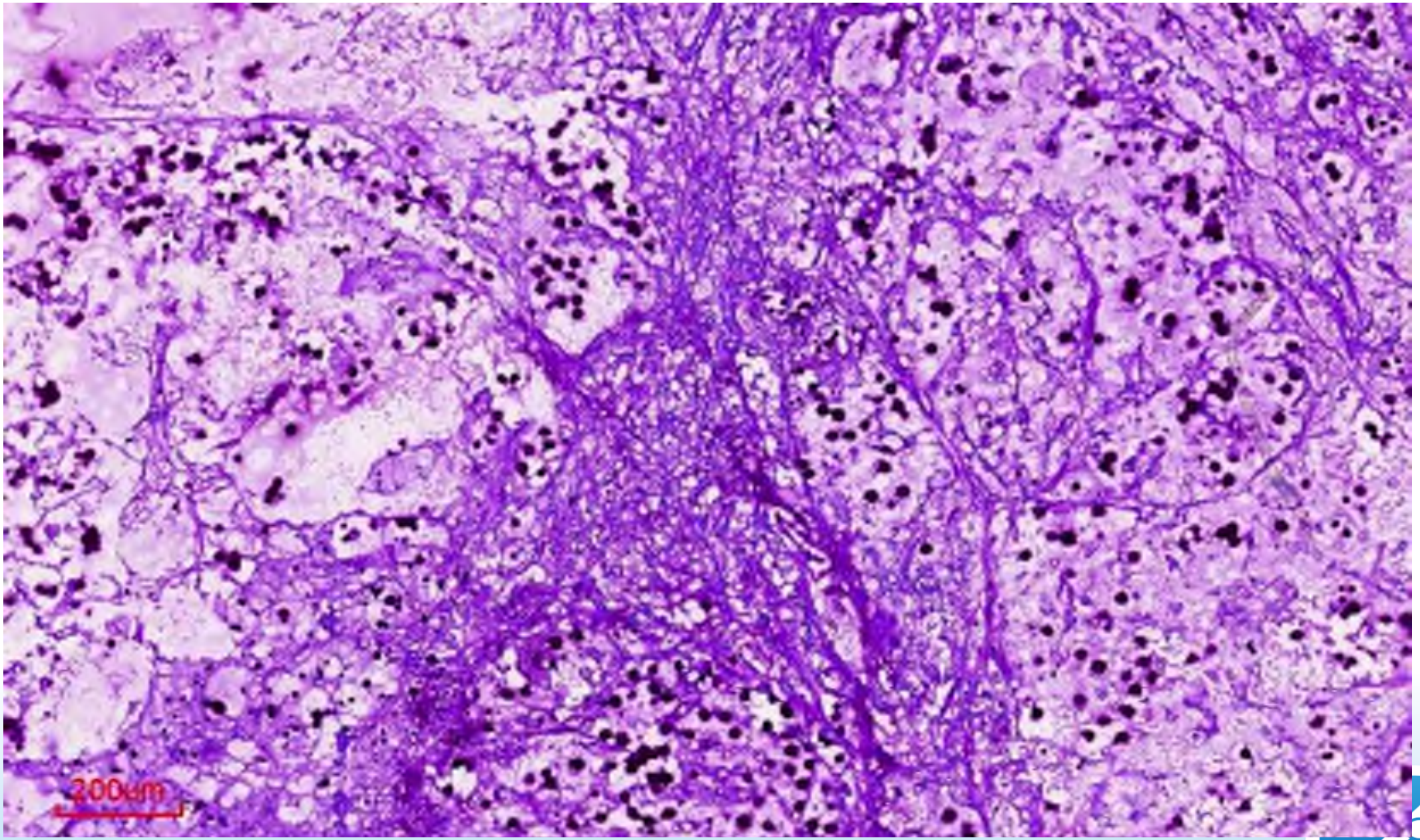
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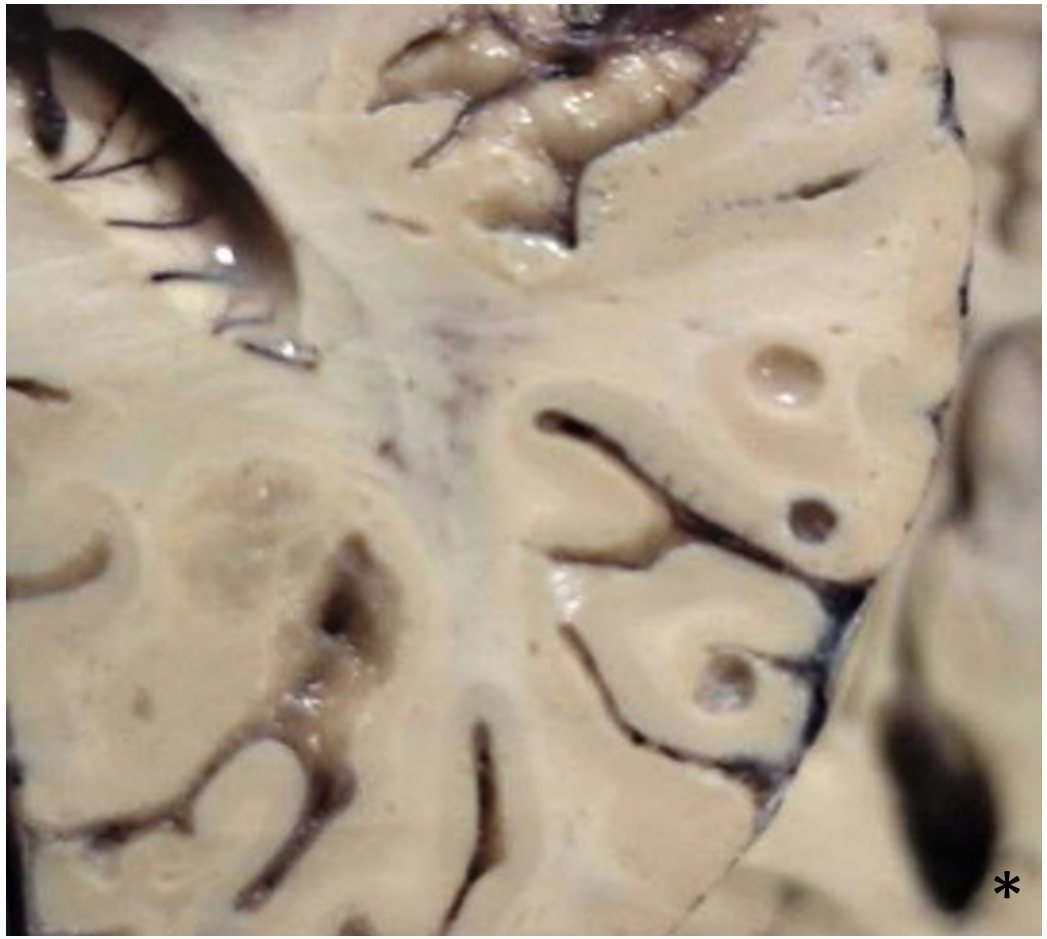
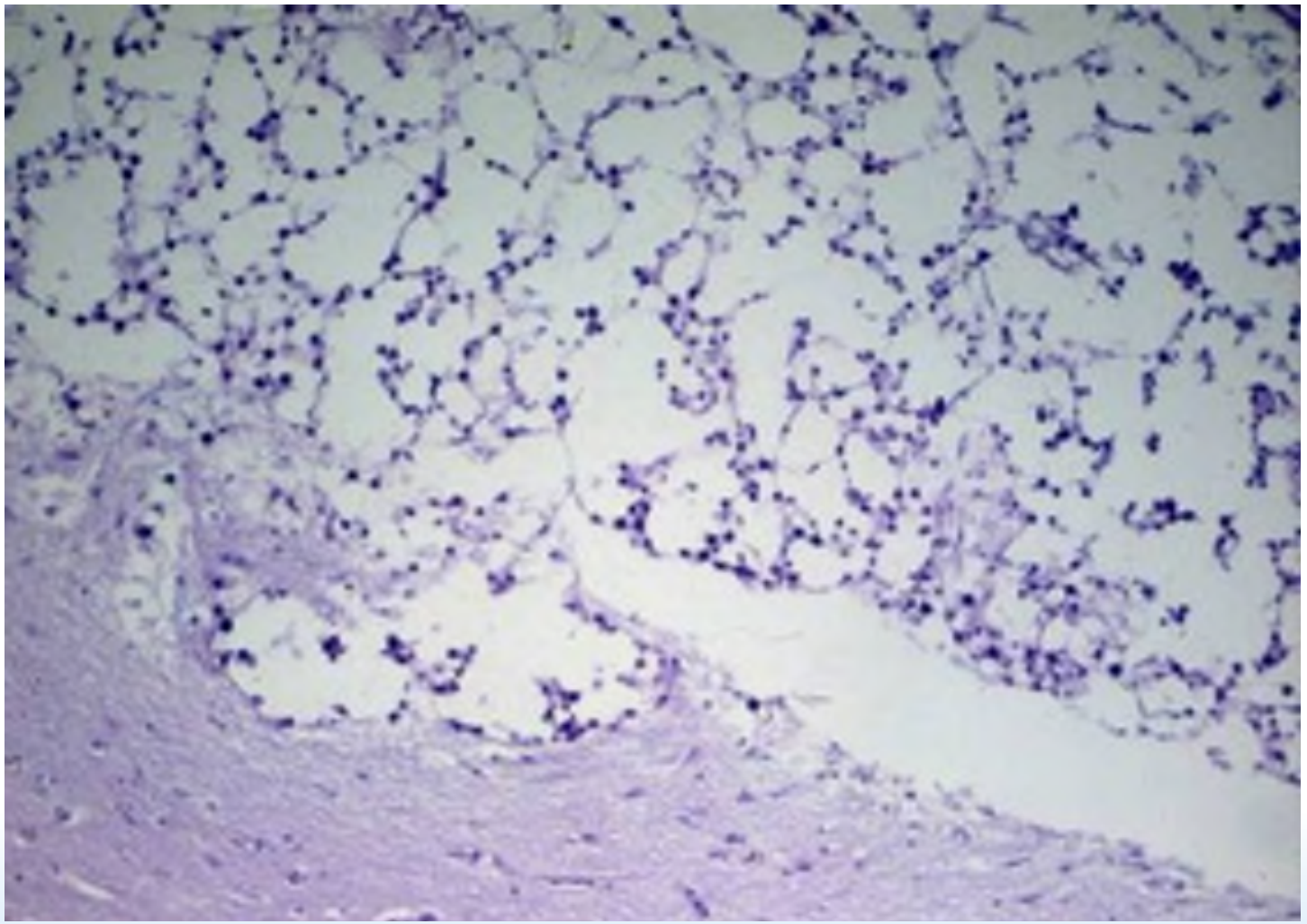
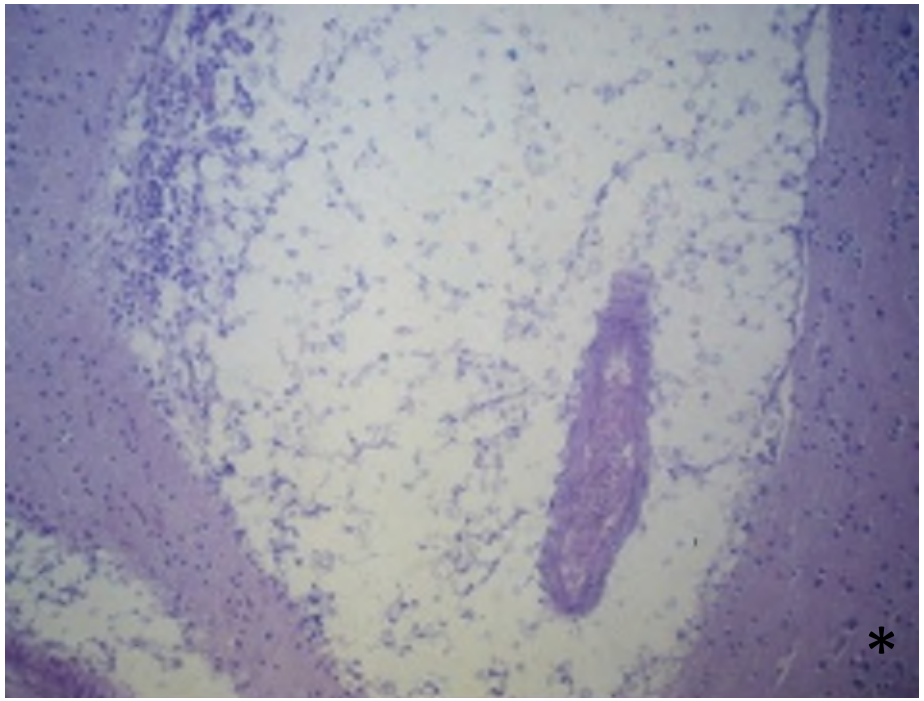
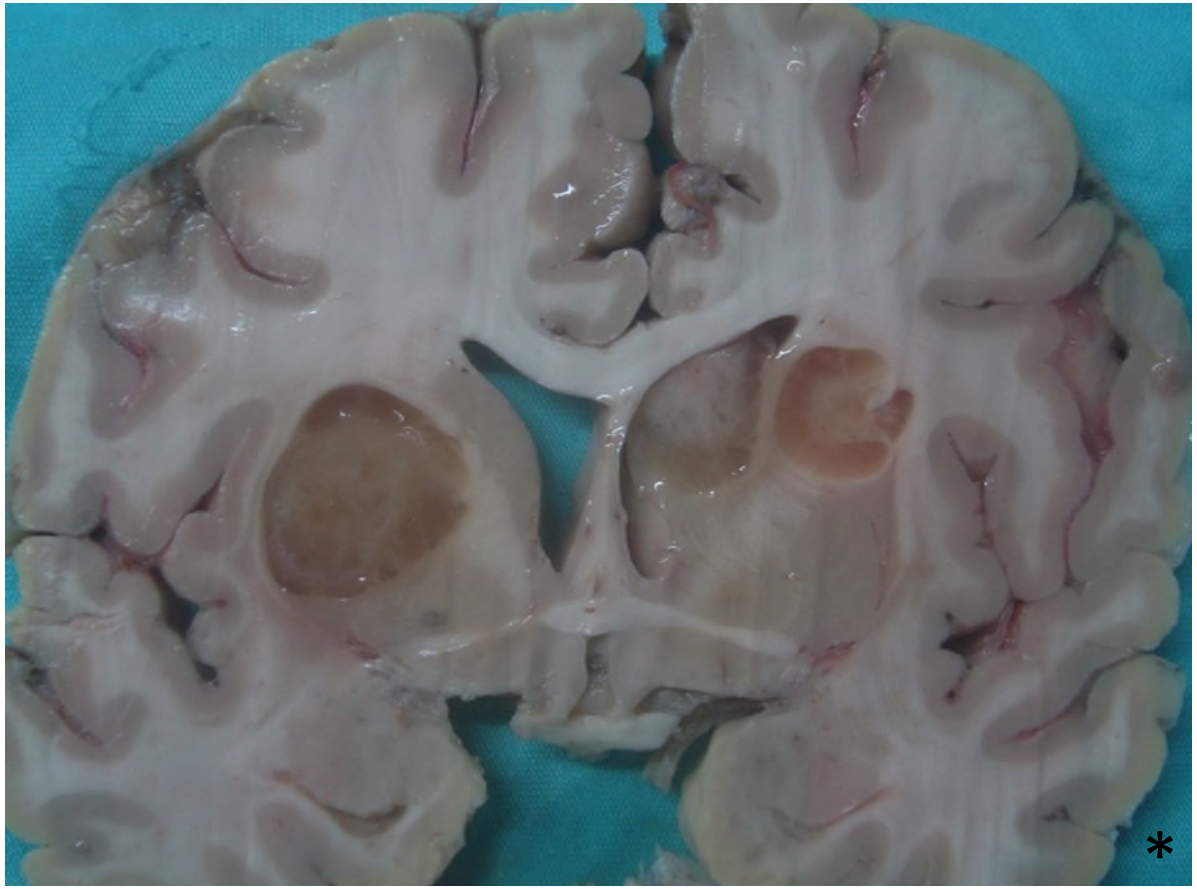
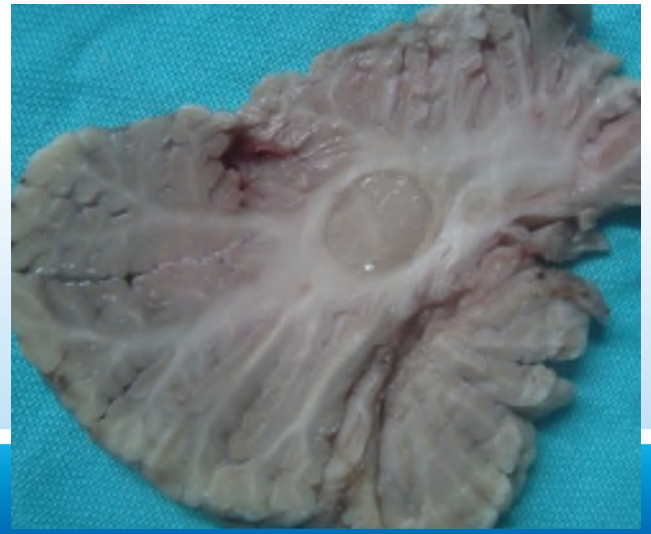


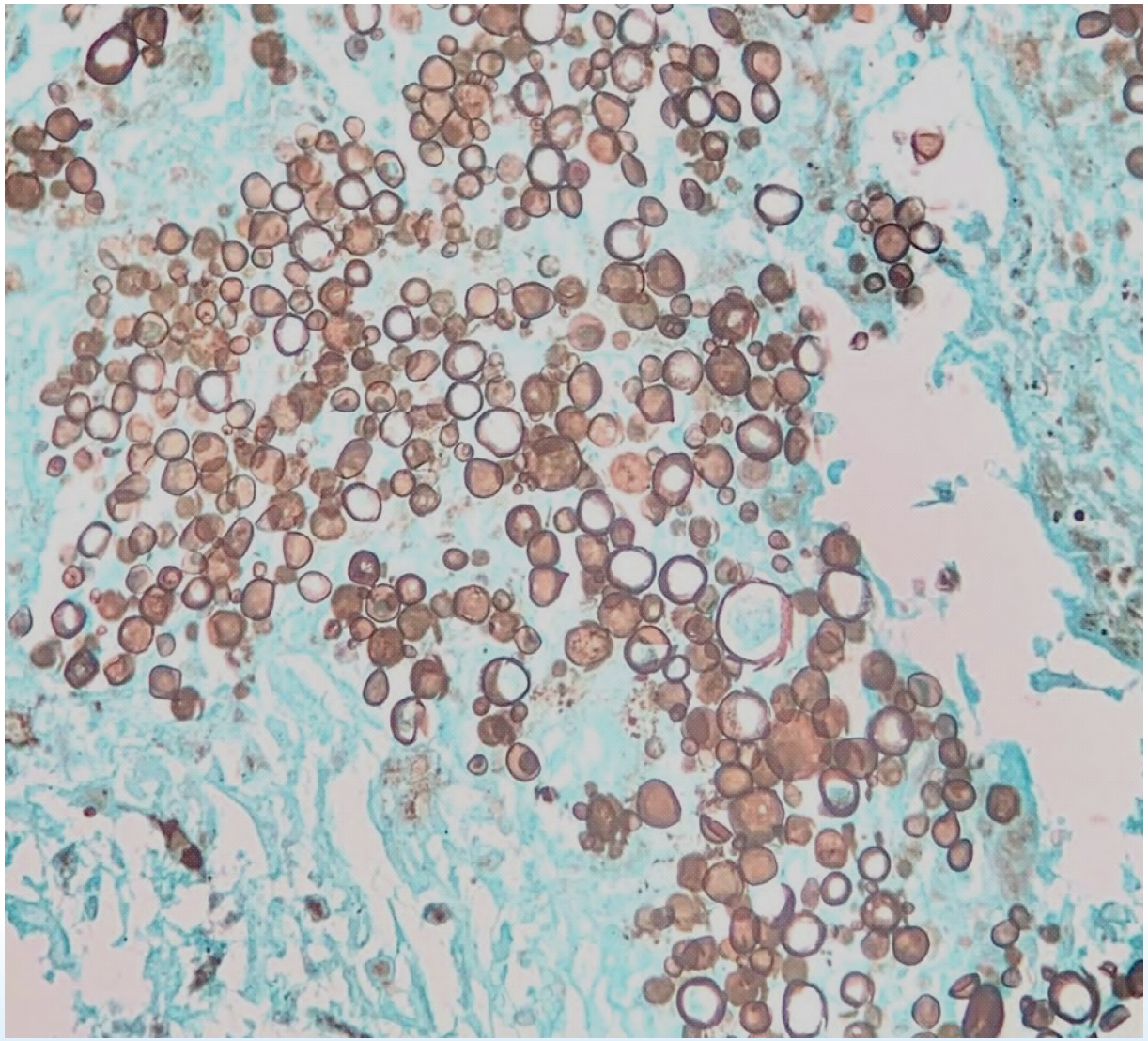






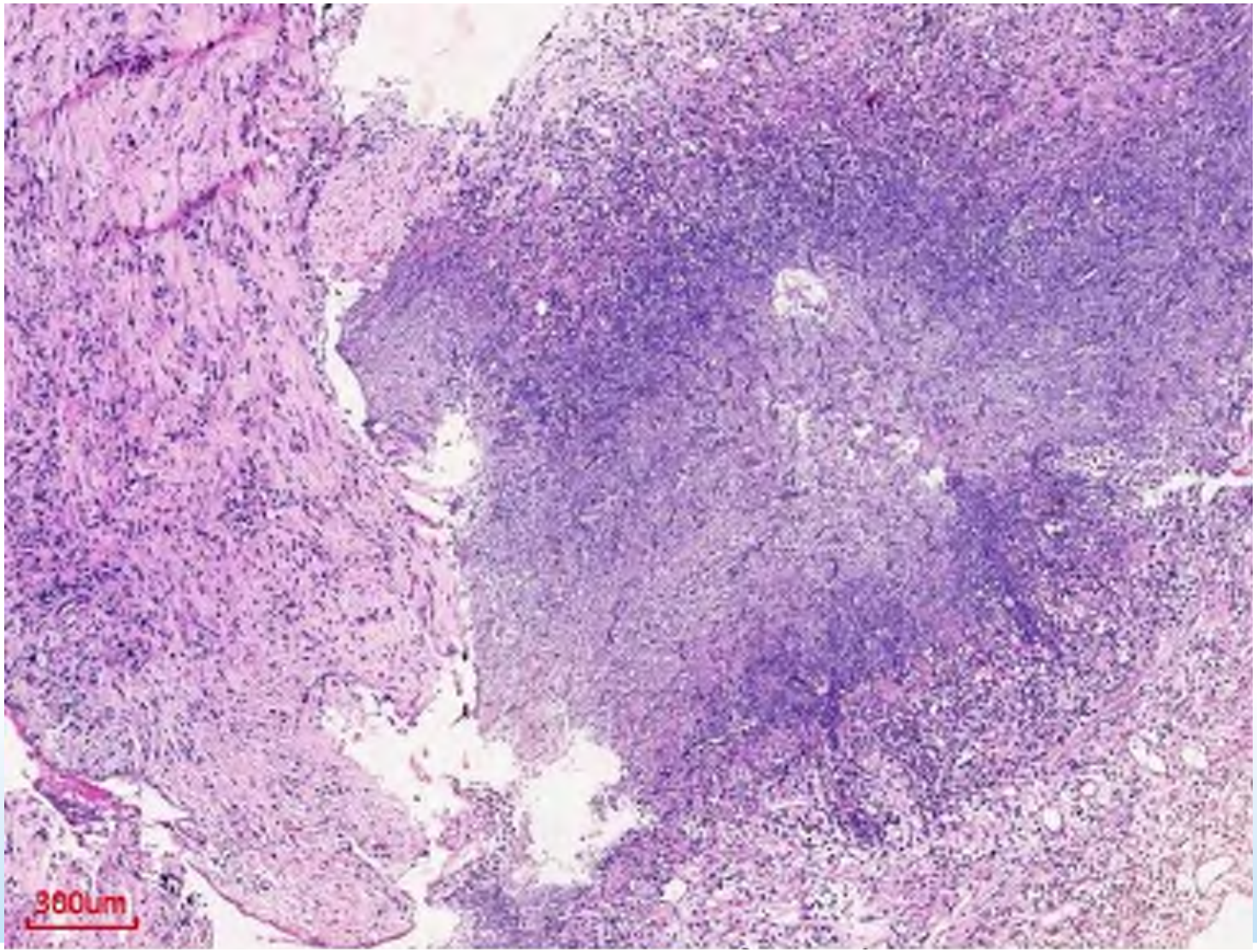


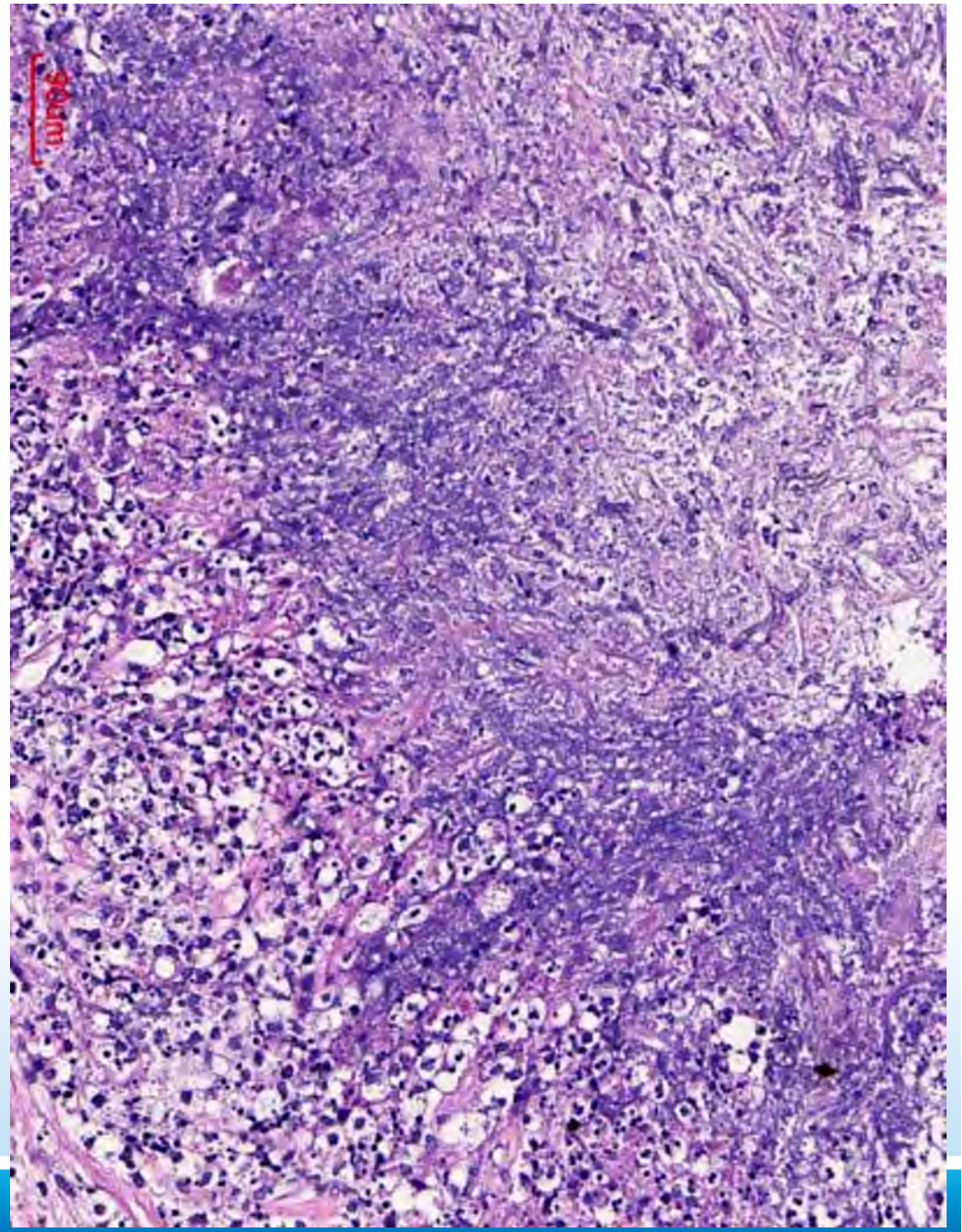
Grocott Metenamine Silver



Courtesy of Dr. F. Andreiuolo

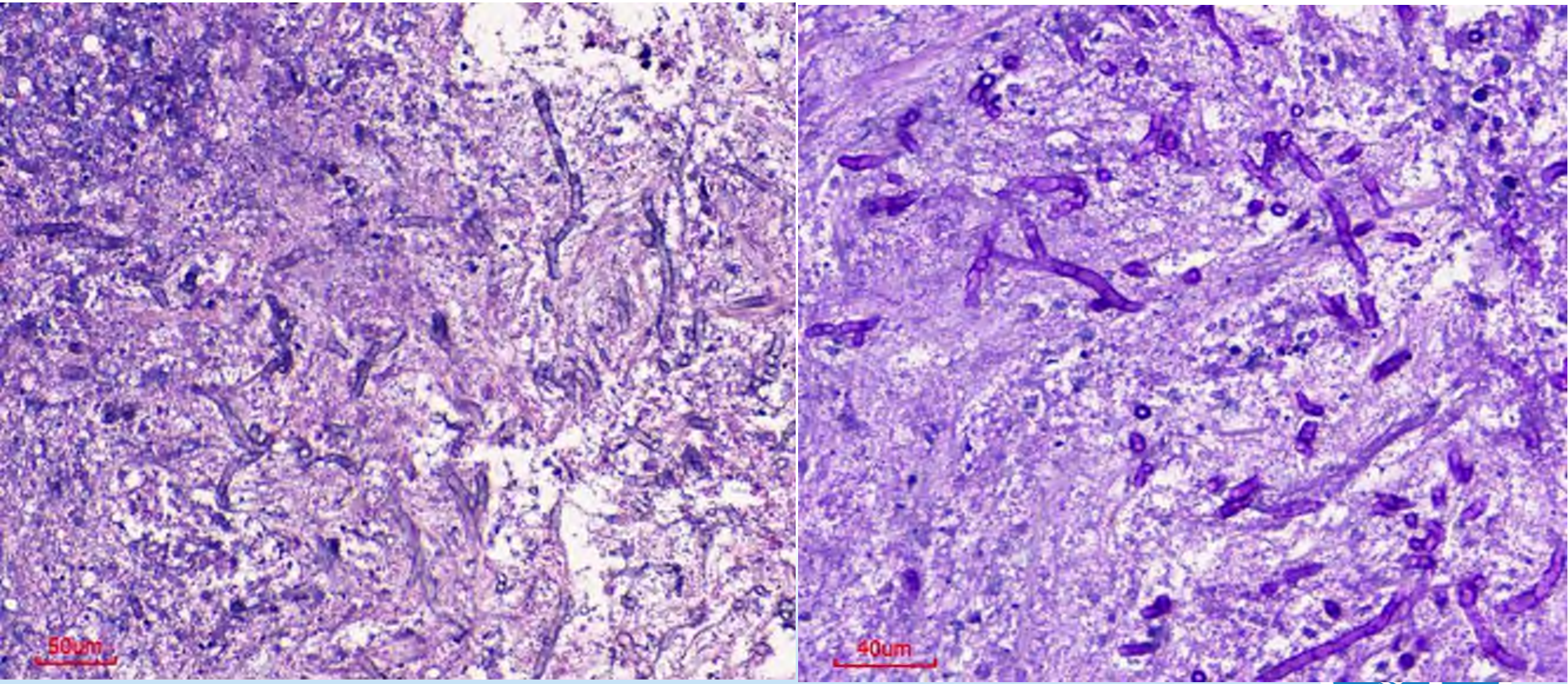
47-year-old HIV+ man – Clinoid tumor





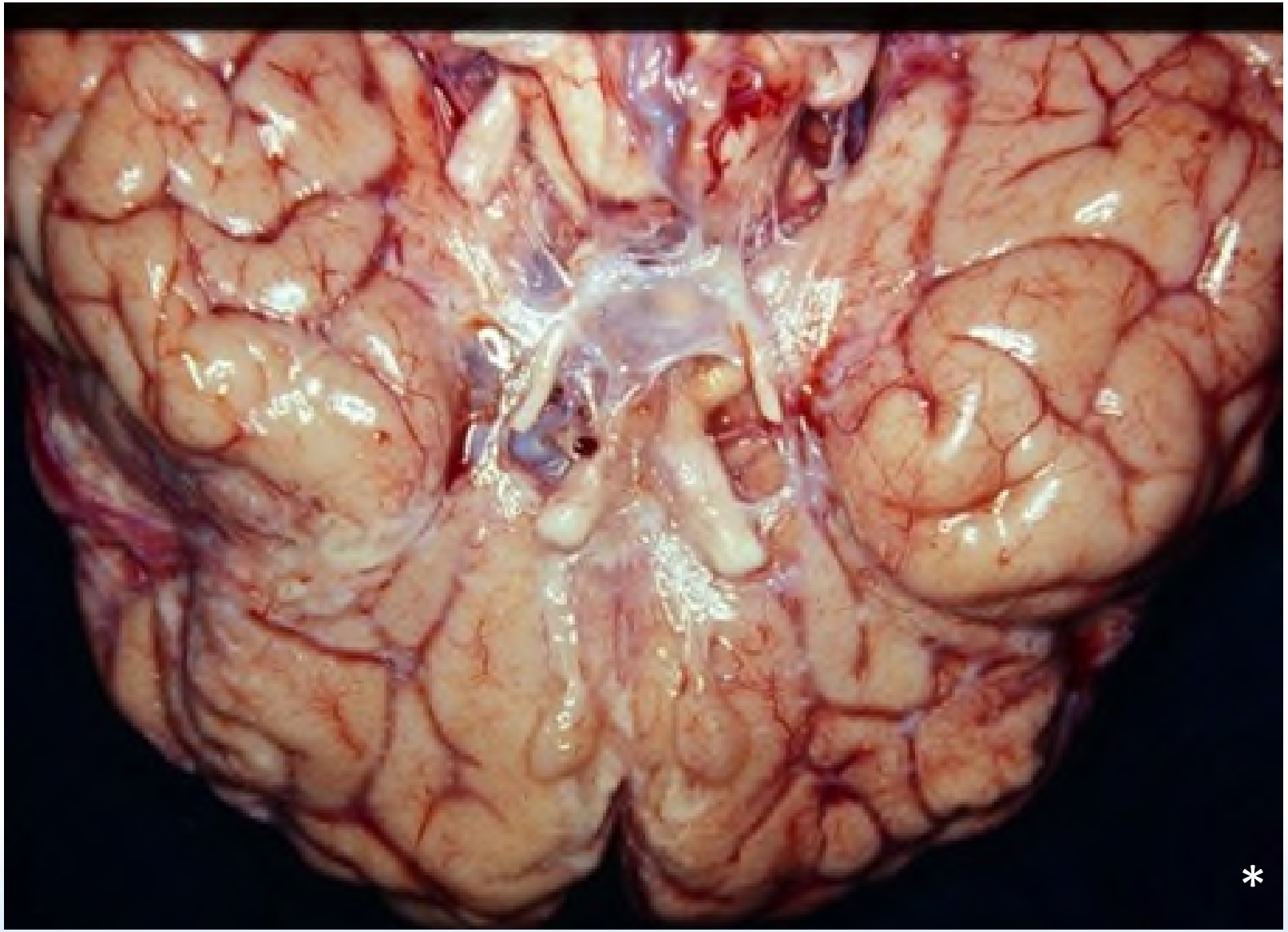
Large septate and branching hyphae - Mucormycosis

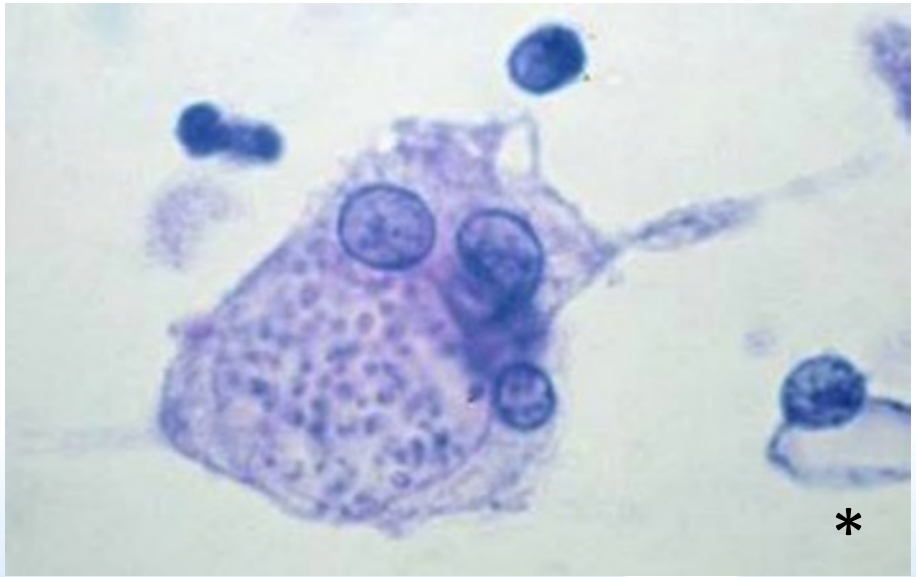
PAS



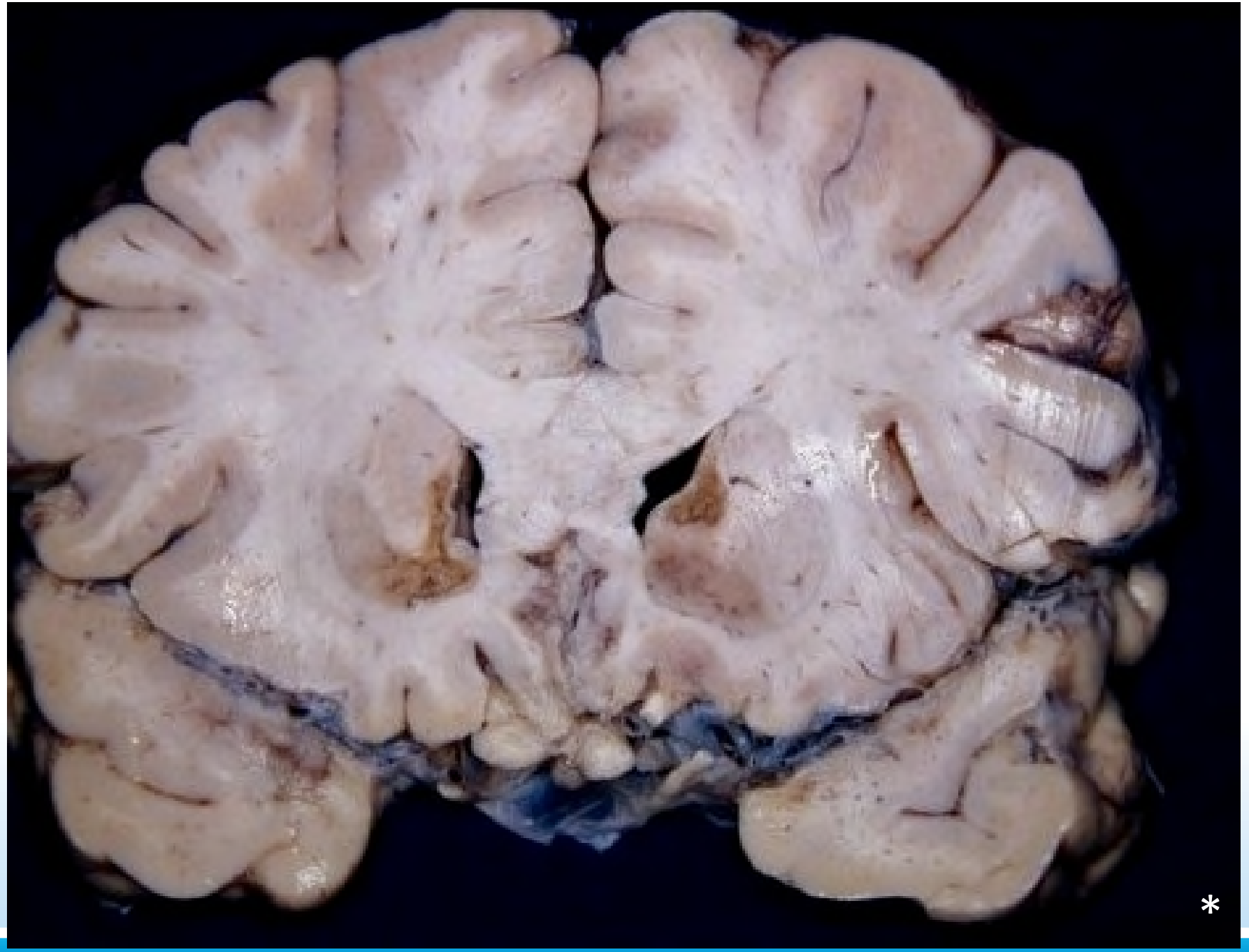
Histoplasmosis

- Histoplasma capsulatum
- Inhaled in infected dust contaminated by chicken, bird or bat excreta
- Lungs are primarily infected, but also mouth, digestive tract and skin
- Frequent involvement of lymphnodes, spleen, liver
- CNS infection is rare





Histoplasmosis – Basal meningitis

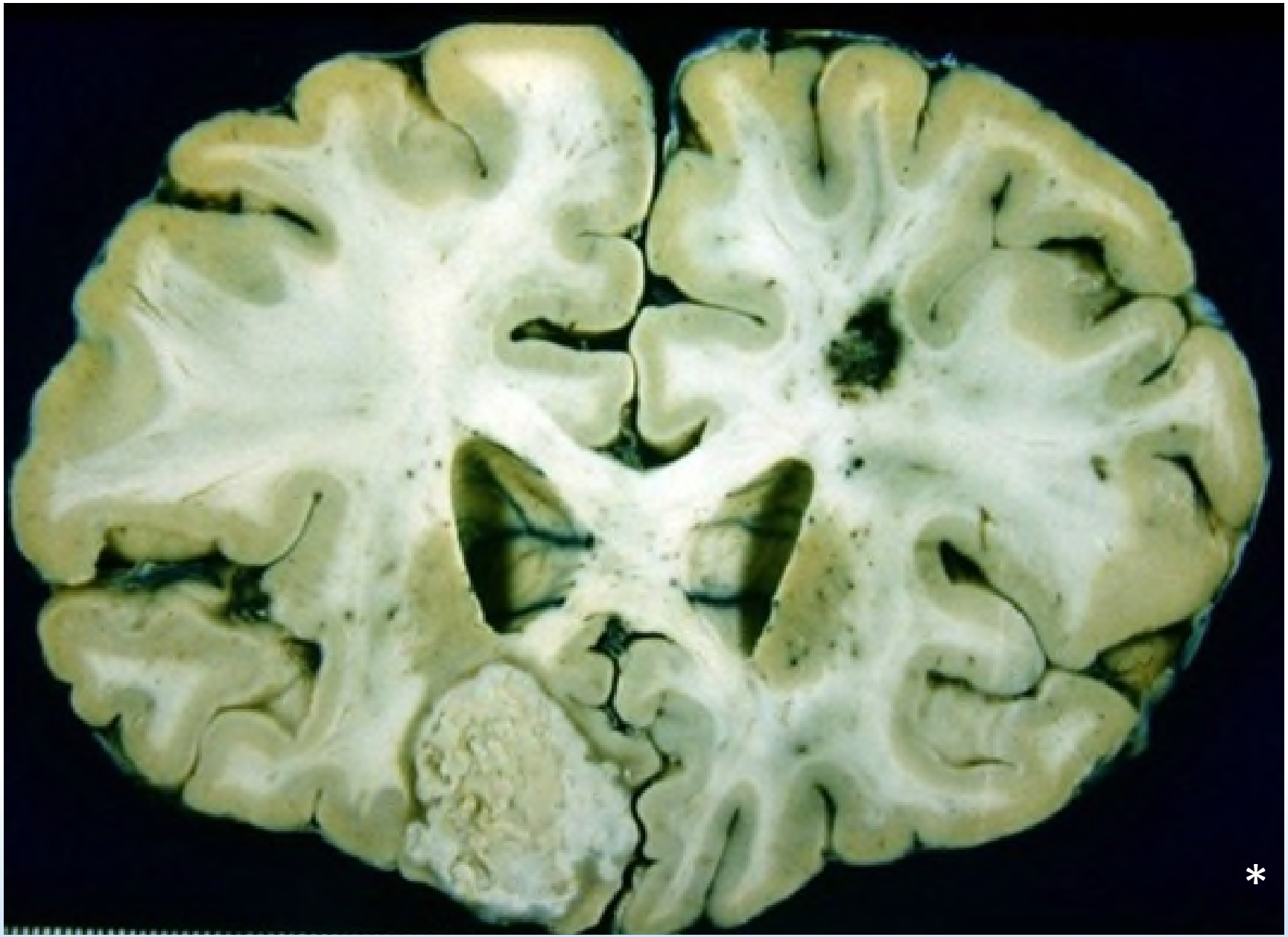


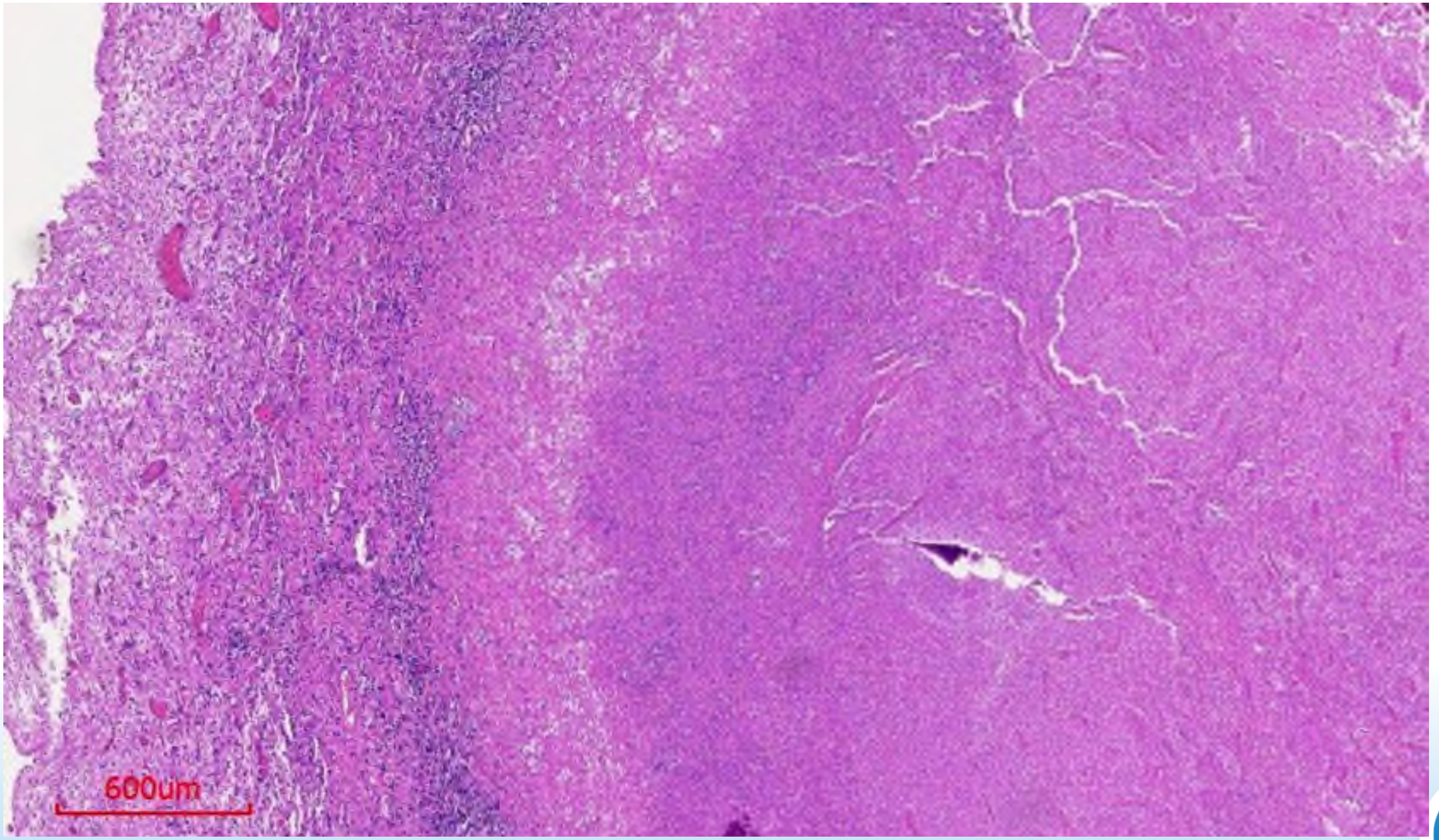
Histoplasmosis

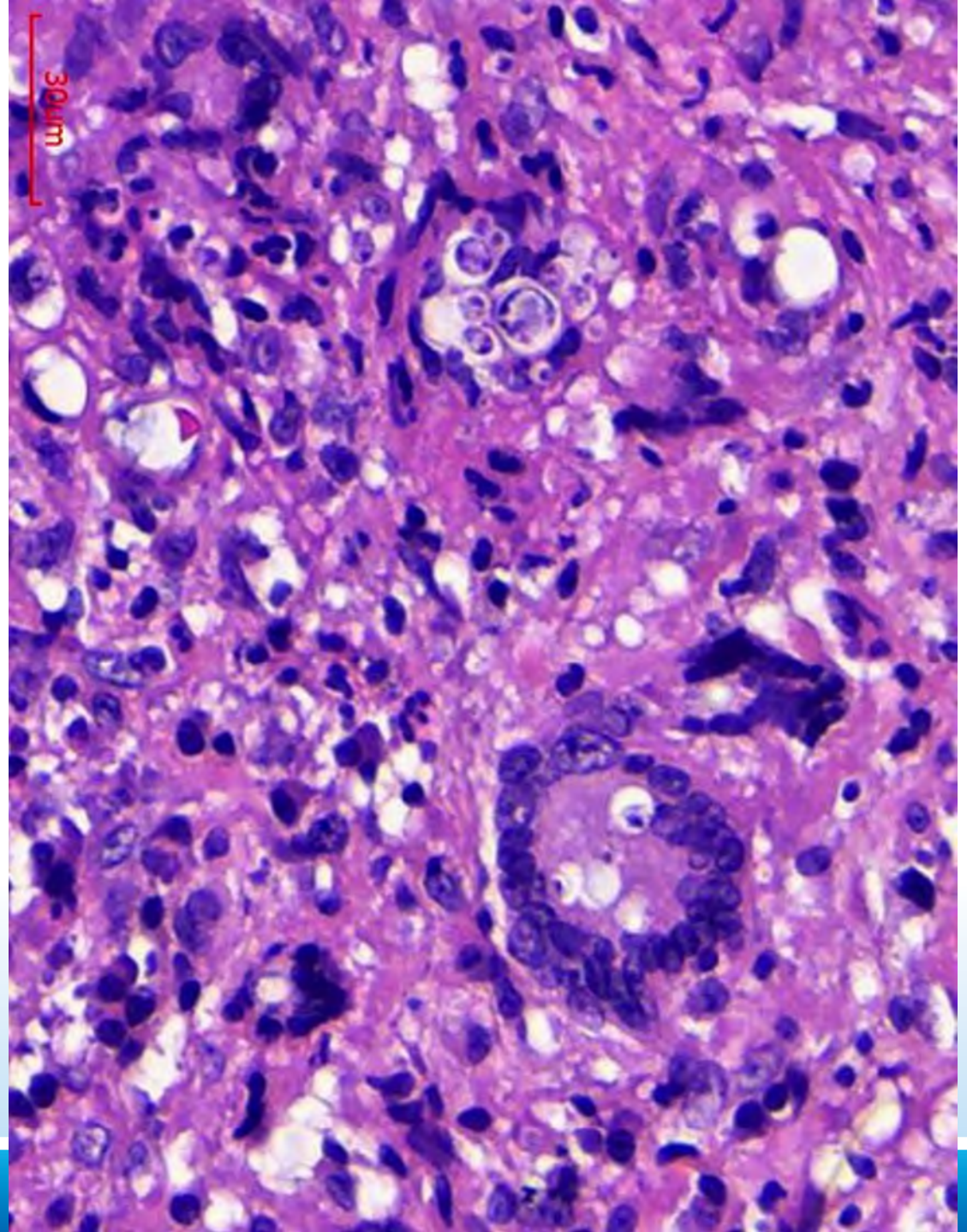
Infarct in basal ganglia

Paracoccidioidomycosis (South American blastomycosis)

- Paracoccidioidis brasiliensis
- Organisms found in soil and vegetation
- Frequent in Brazil, Venezuela and Colombia
- Preferential sites: lungs, oral and nasal mucosae, lymphnodes
- CNS involvement is not frequent




600um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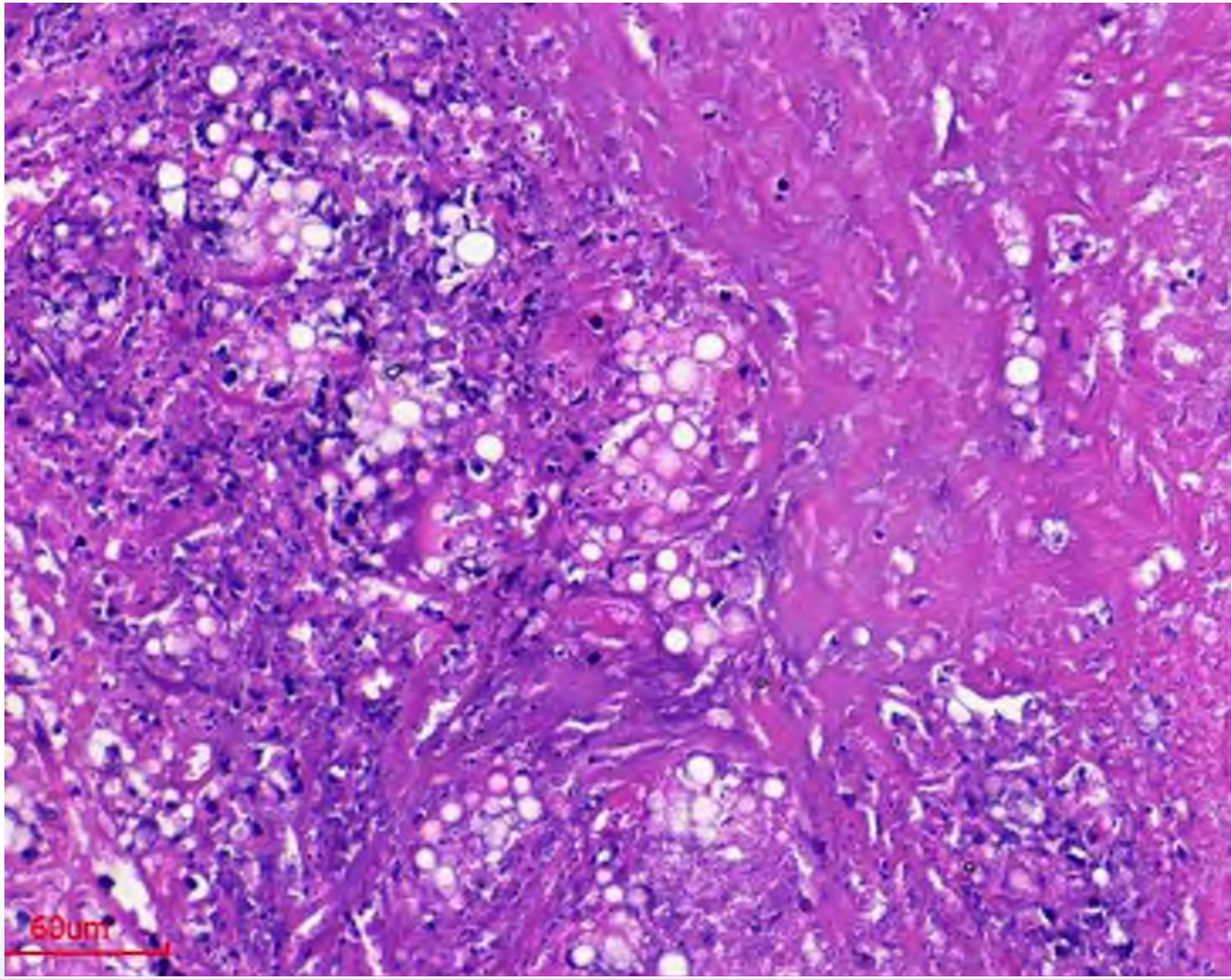
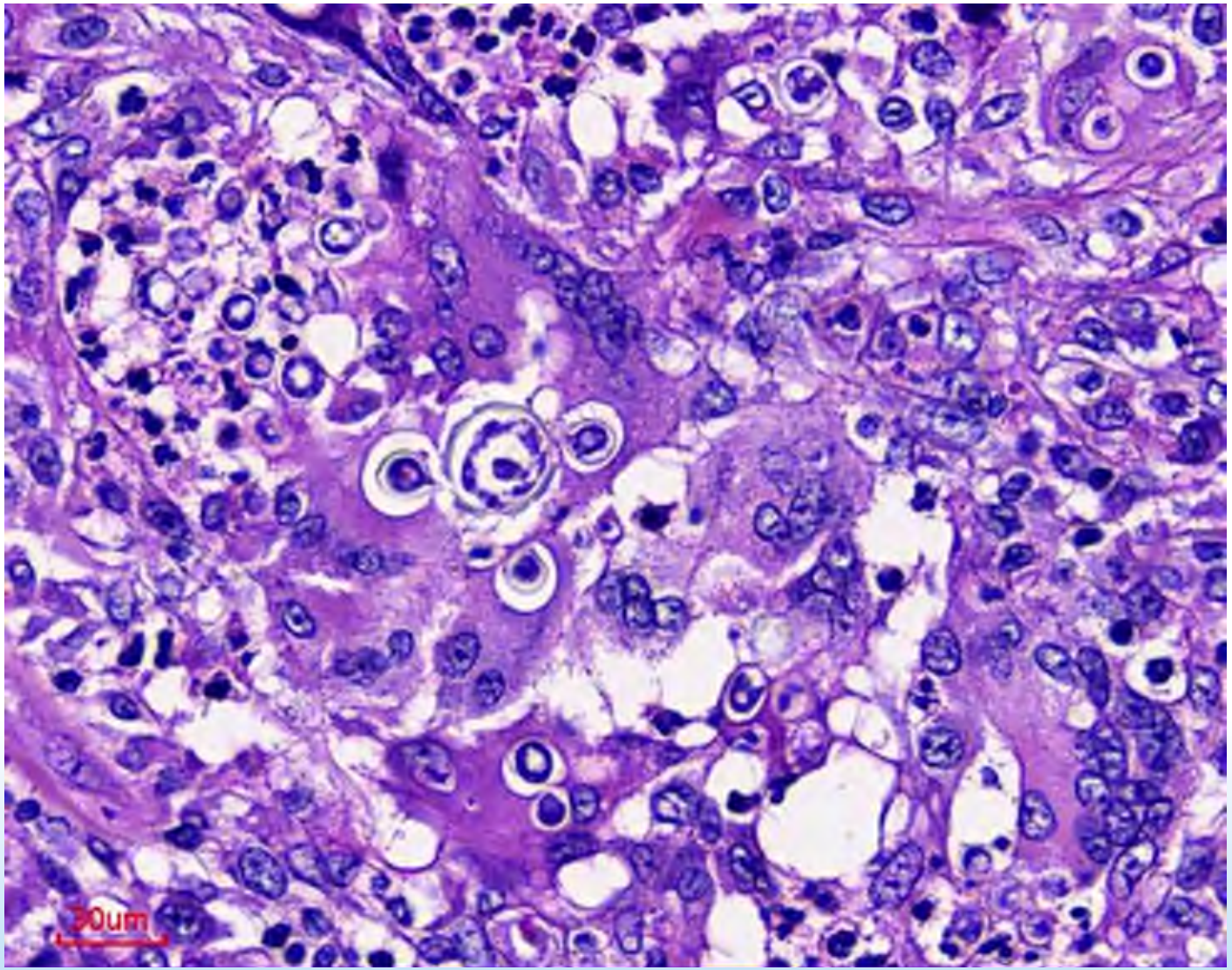
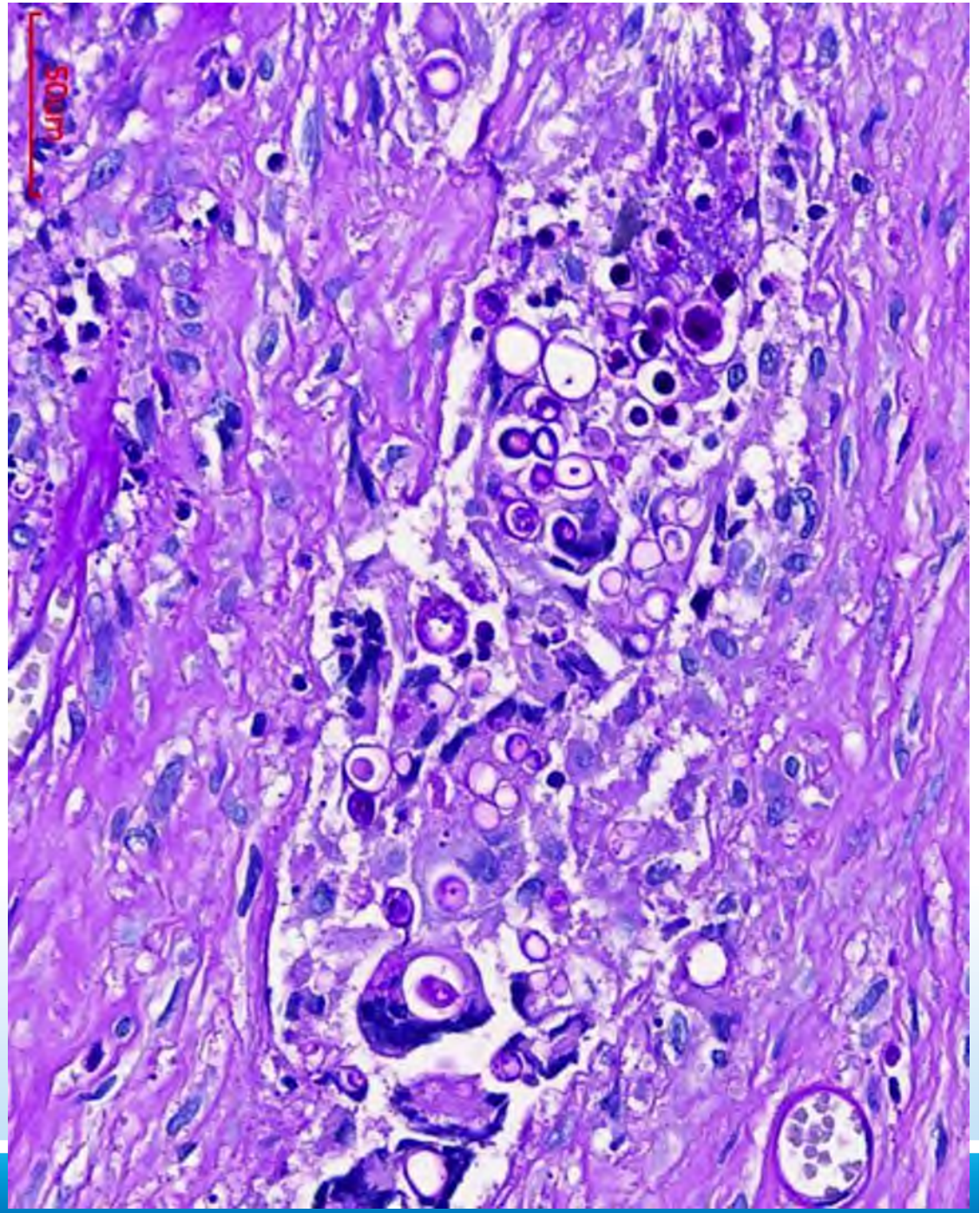
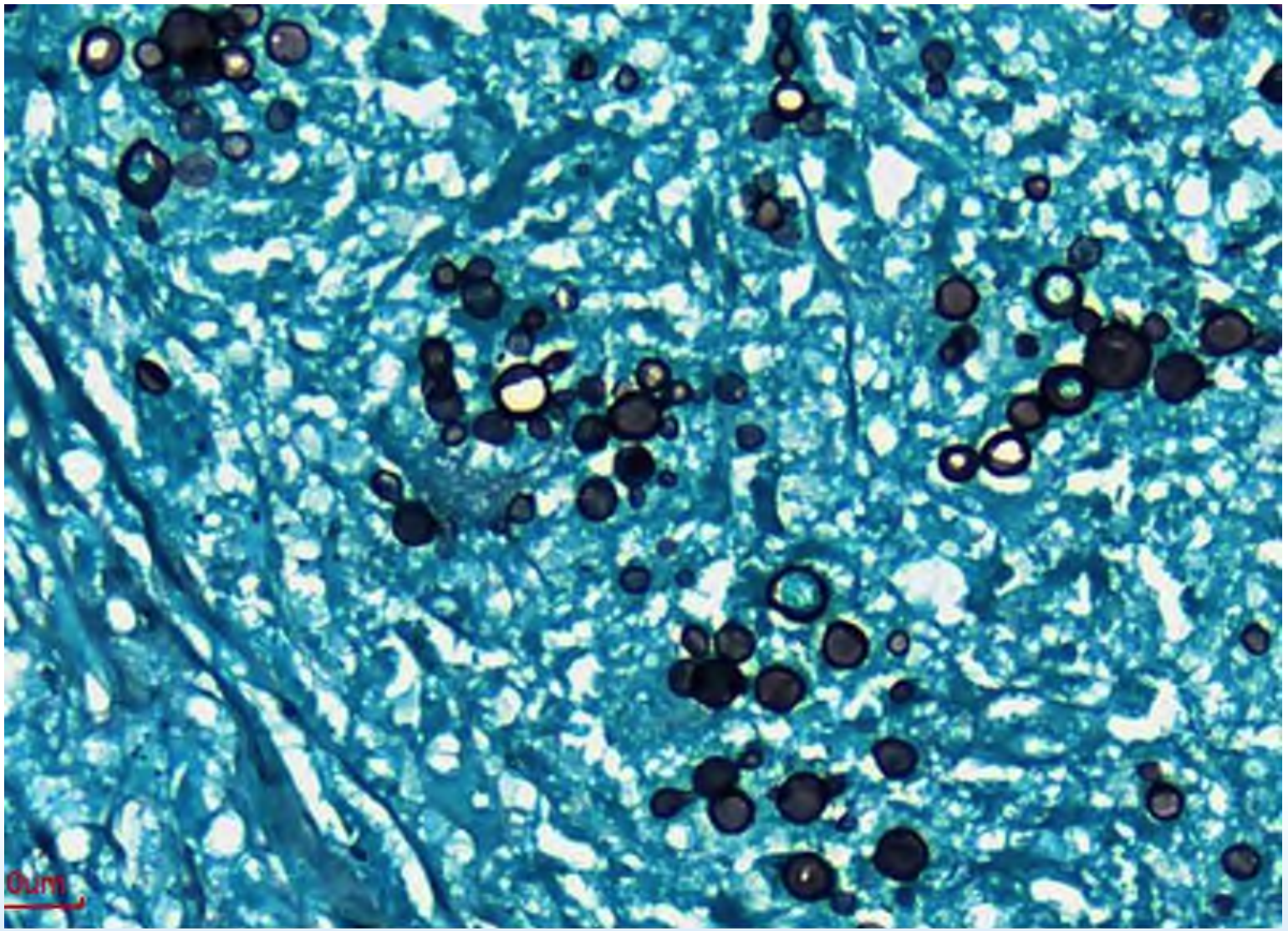

60um

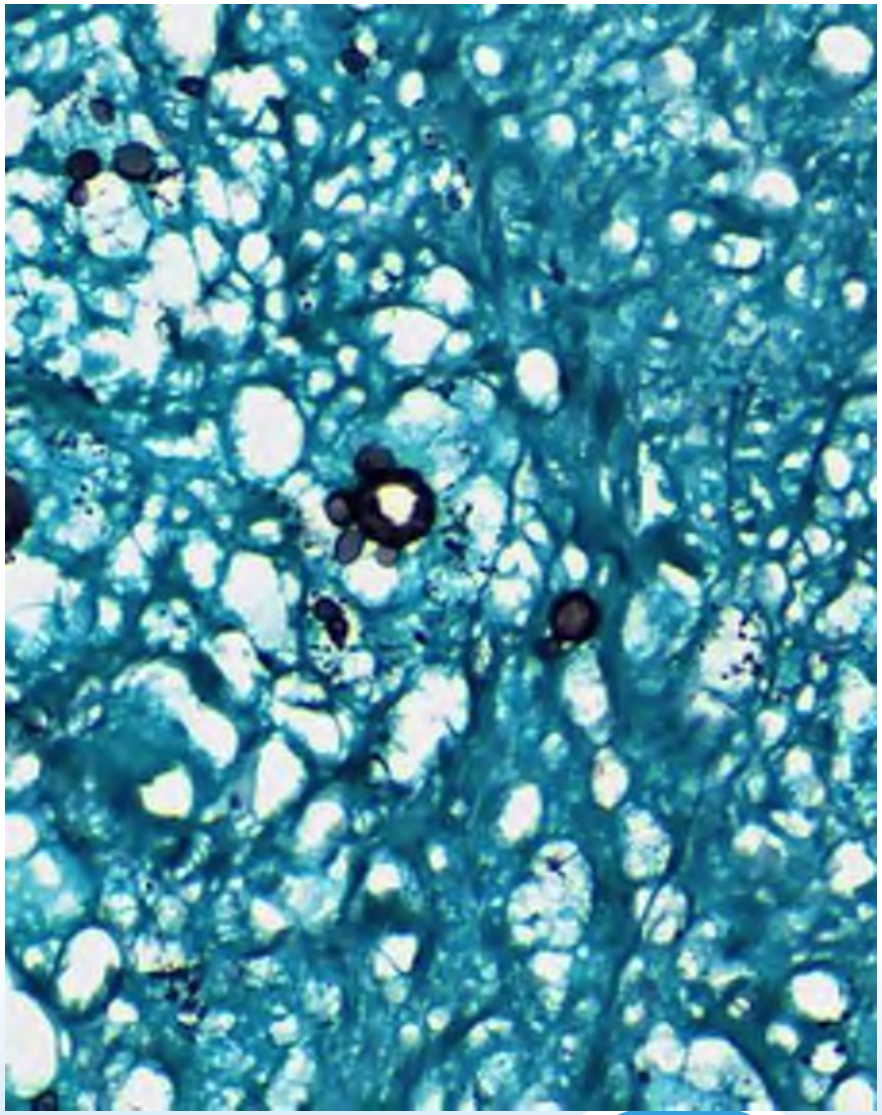
PAS



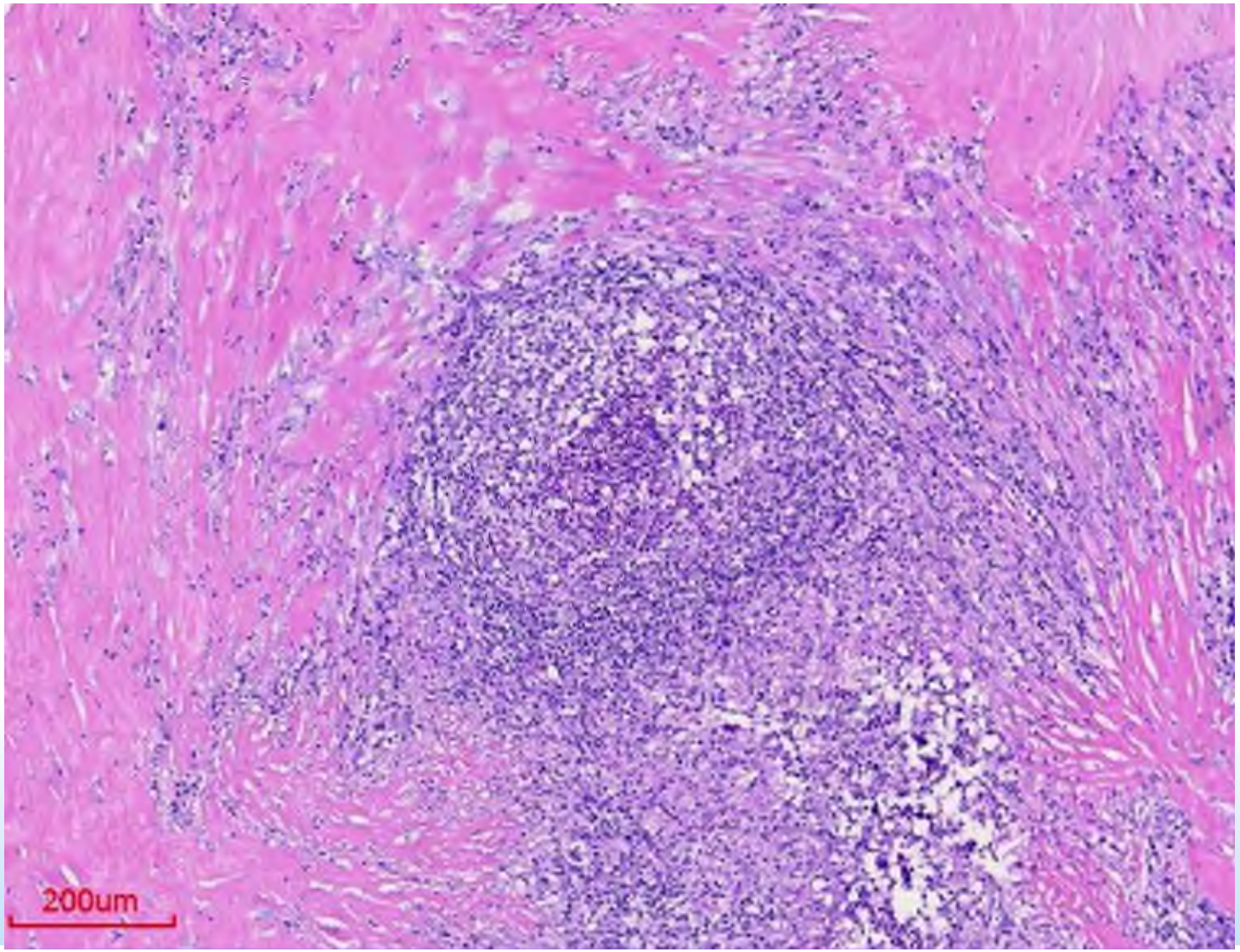


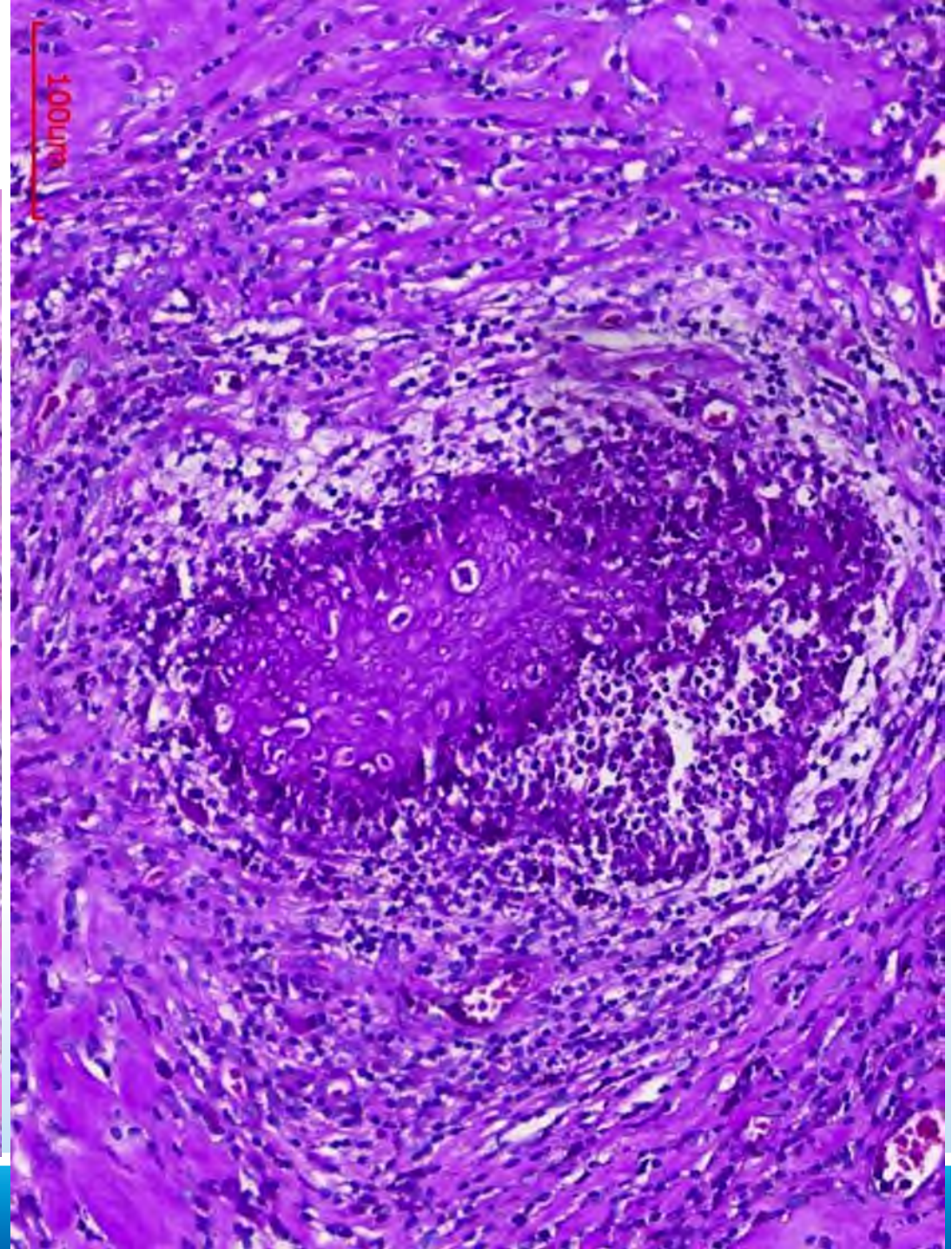
Grocott Metenamine Silver



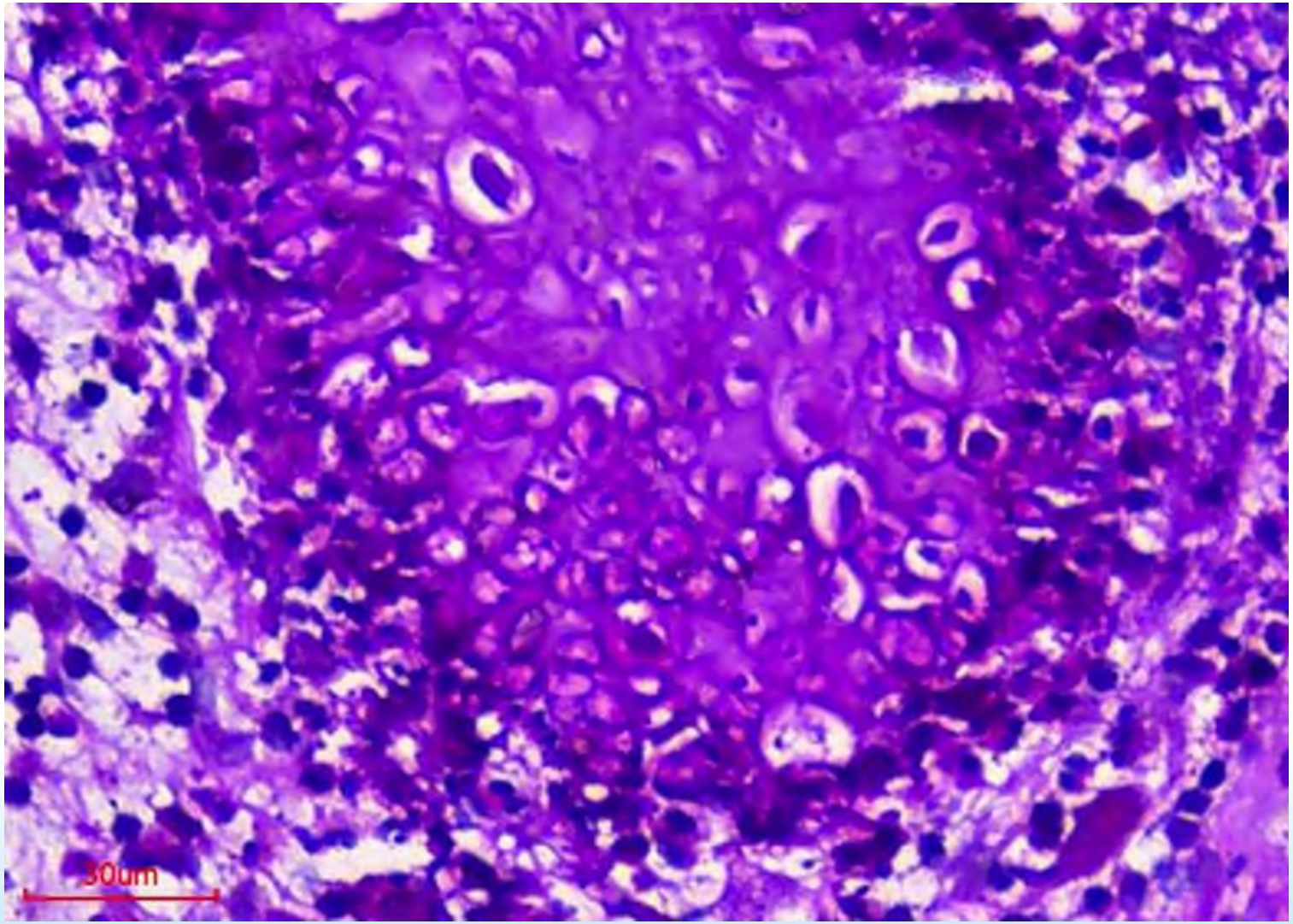


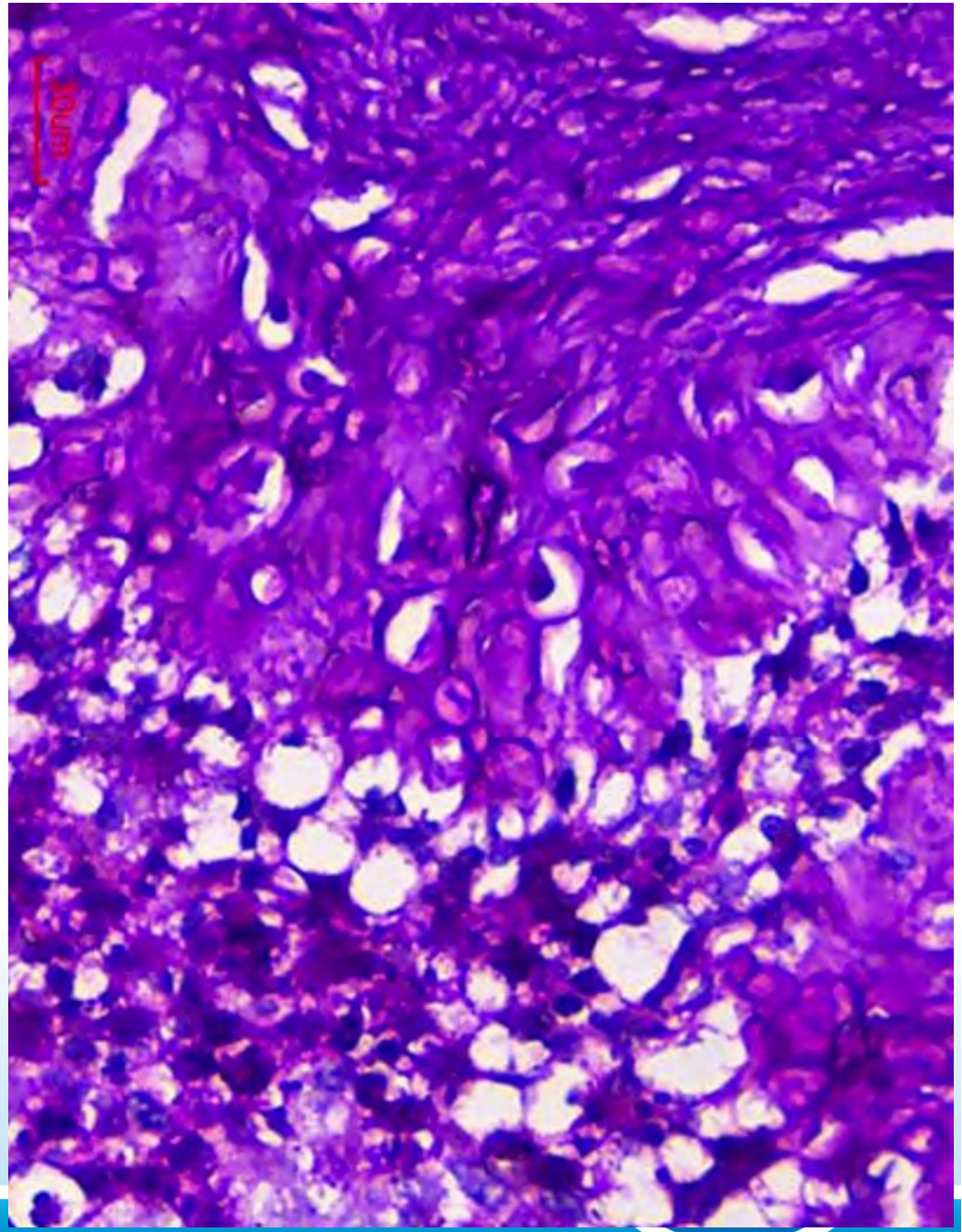
Unusual presentation of fungal infection
50-year-old man with a frontal cerebral tumor





Mycetoma





Etiology

Bacterial: Pyogenic (Gram + / -), Tuberculosis, Syphilis

Fungal: Cryptococcosis, Histoplasmosis, Mucormycosis, Aspergillosis, Paracoccidioidomycosis

Parasitic: Protozoa: Toxoplasmosis, Trypanosomiases, Malaria, Amebiasis

Helminths: Cestodes: Cysticercosis, Hydatidosis

Nematodes: Strongyloidiasis

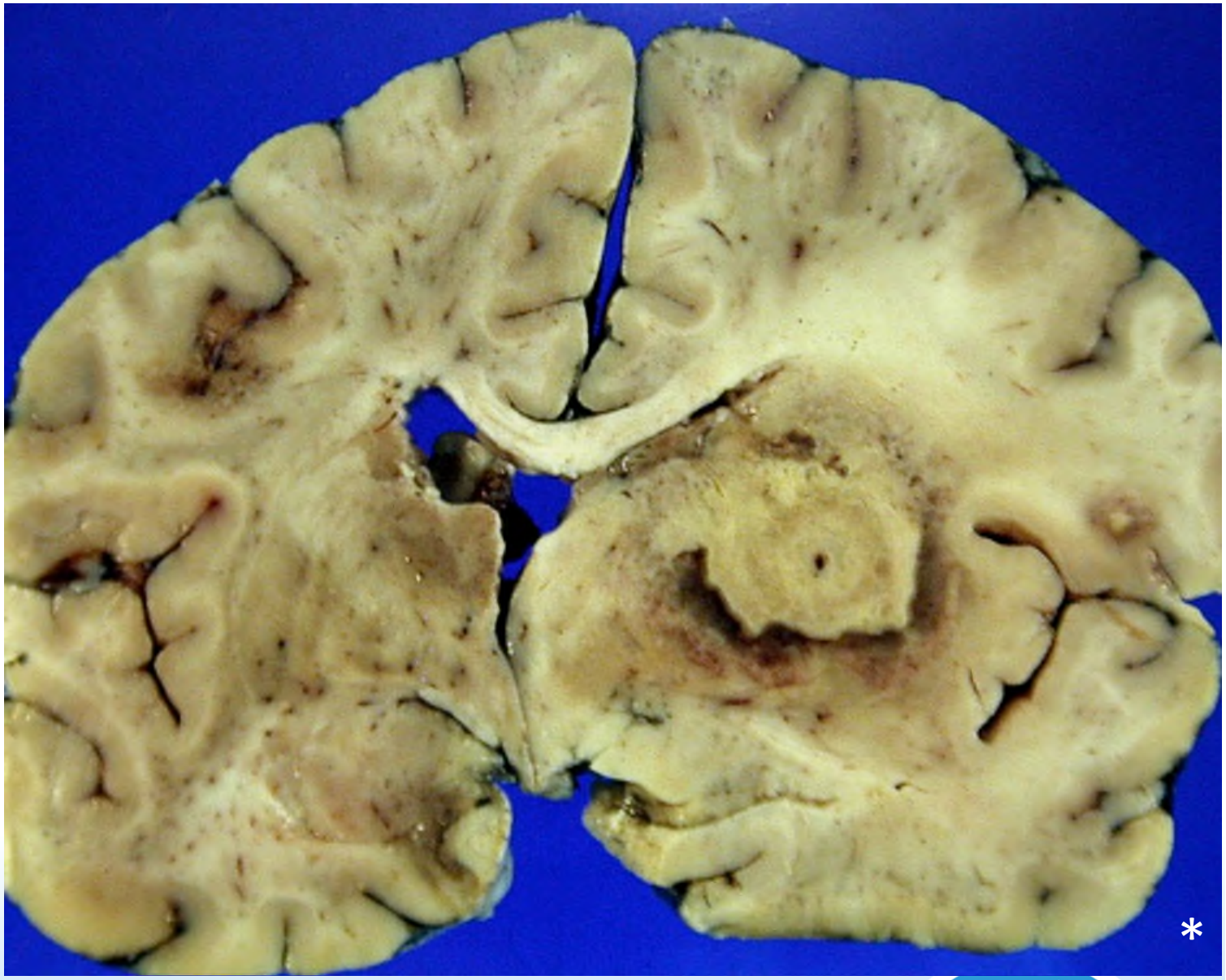
Trematodes: Schistosomiasis

Viral: Arboviroses (Dengue, Zika), Herpes, CMV, HIV, HTLV1, Measles, Poliomyelitis, PML, Rabies.

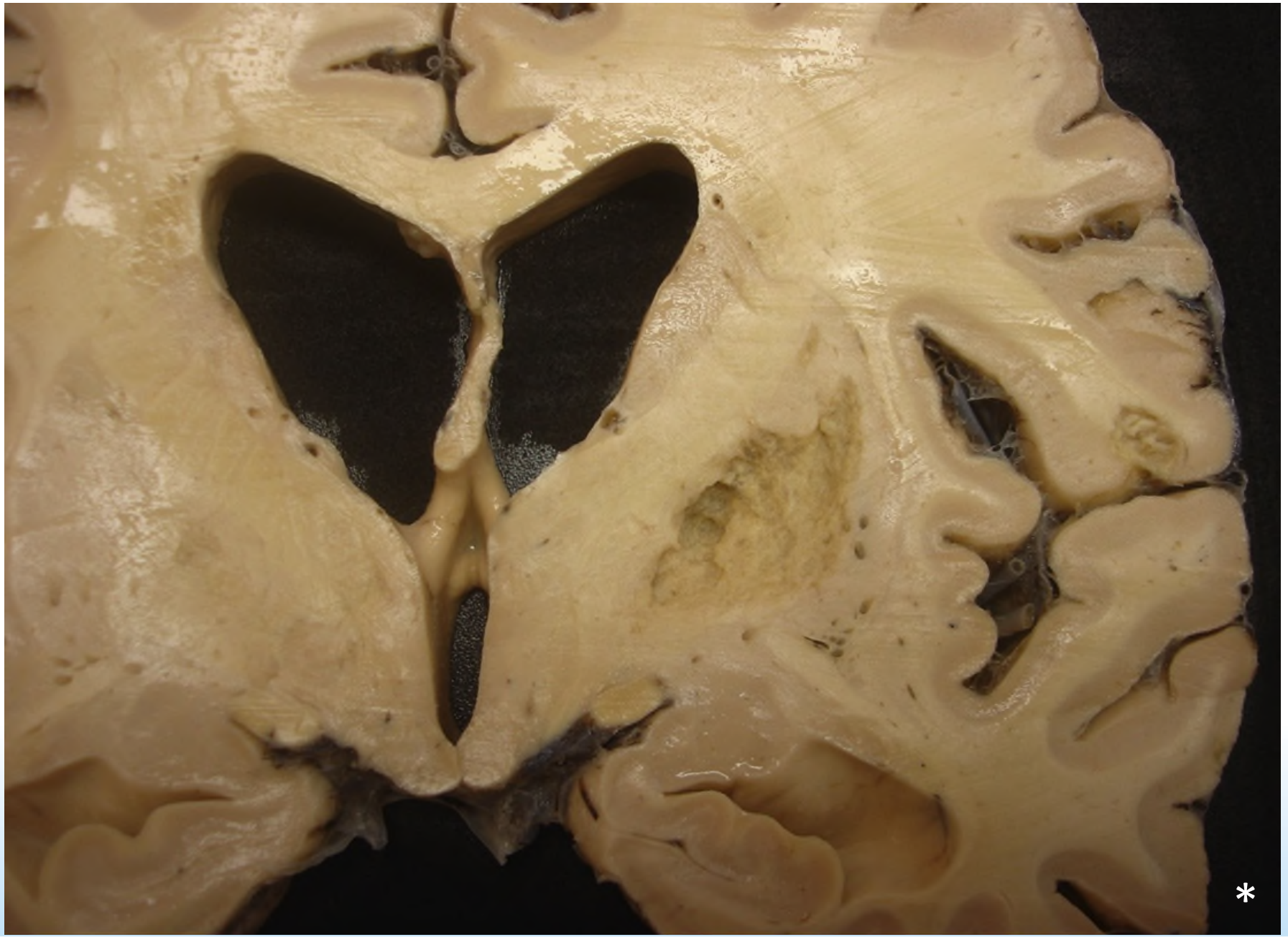
CEREBRAL TOXOPLASMOSIS

Occurs only in immunodefficient patients

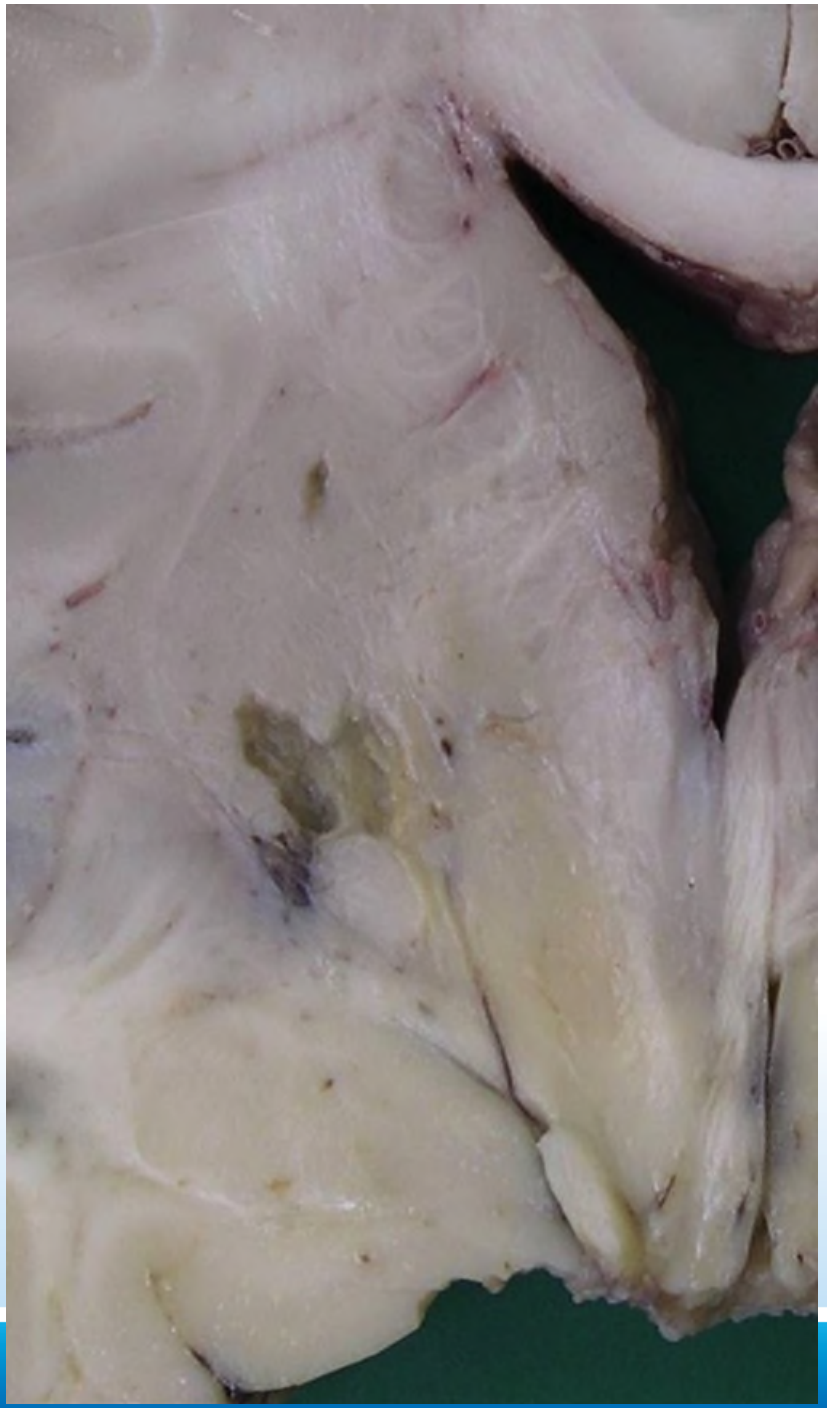
- Acquired
  - –Pseudo-tumoral
  - –Encephalitic
- Congenital

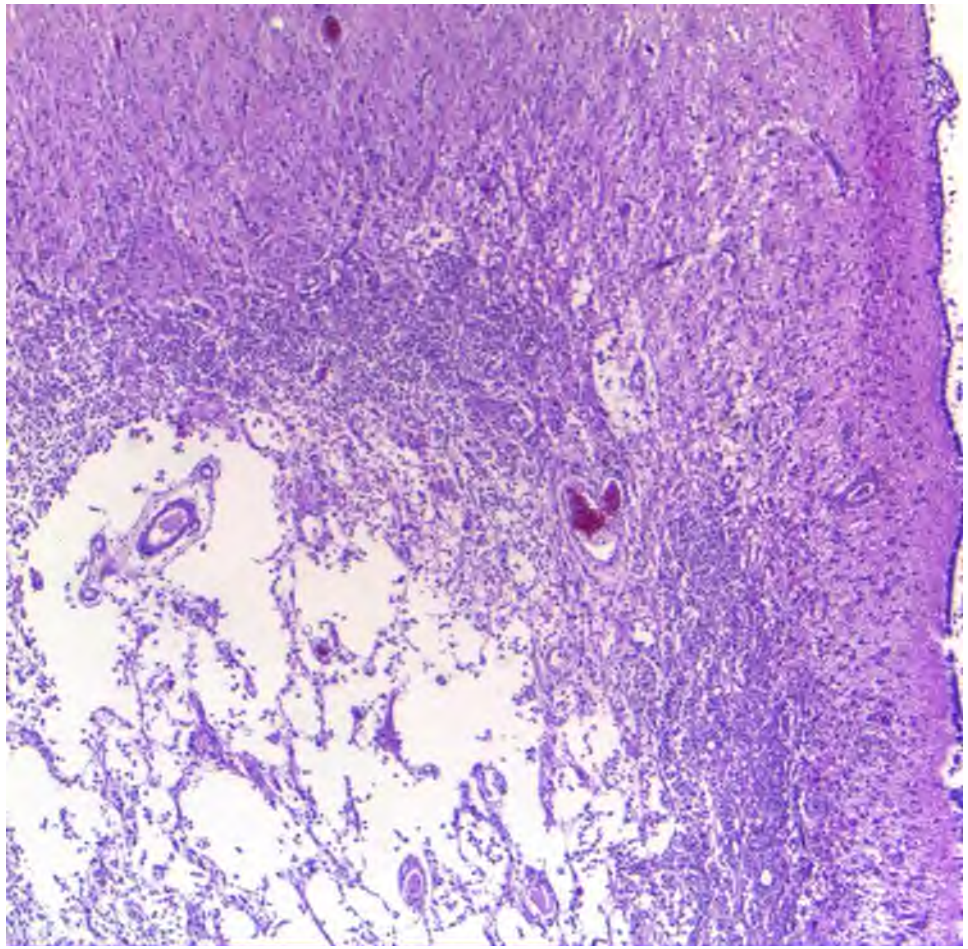


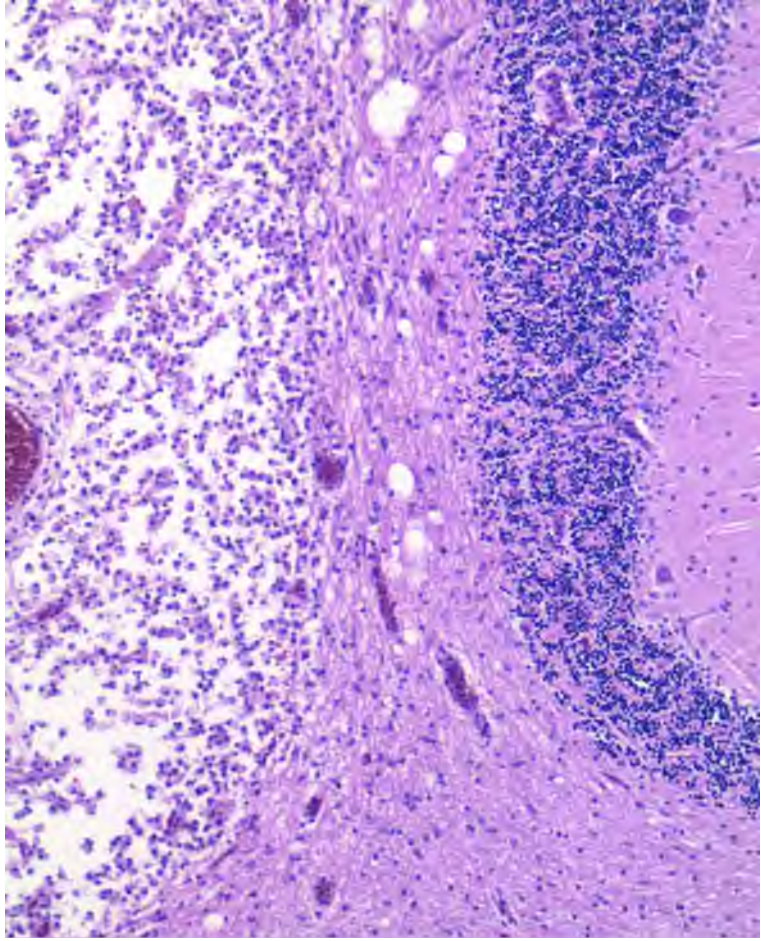
Patient with AIDS who died in 1986



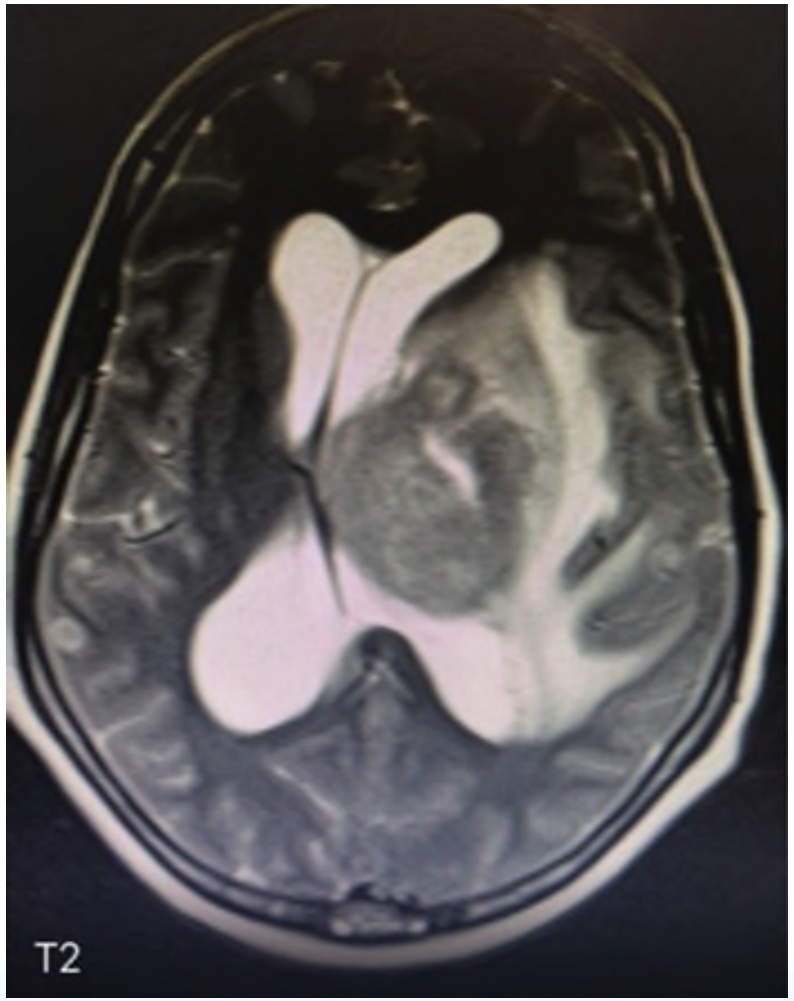
HIV patient who had Toxoplasmosis and died in 2001

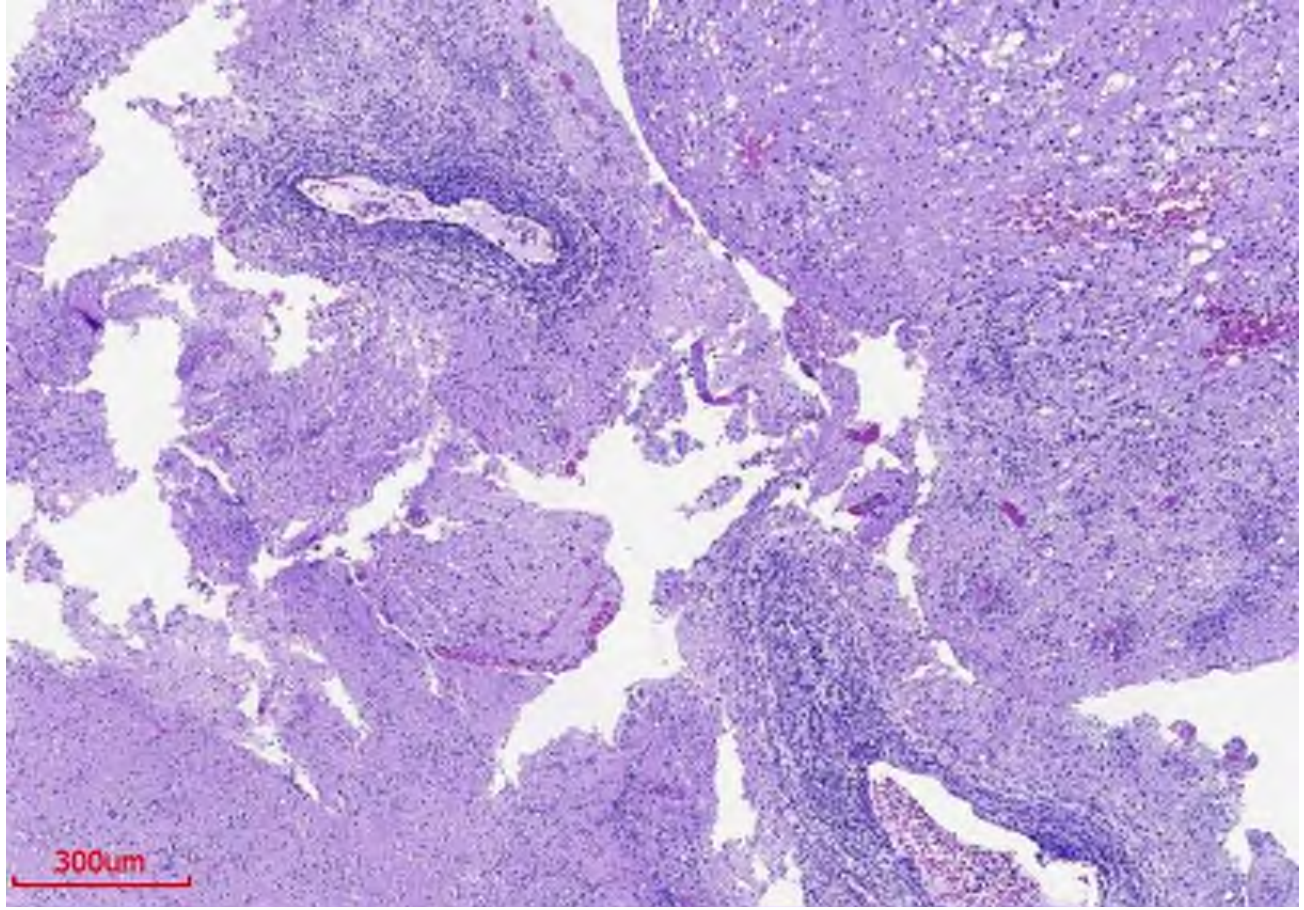


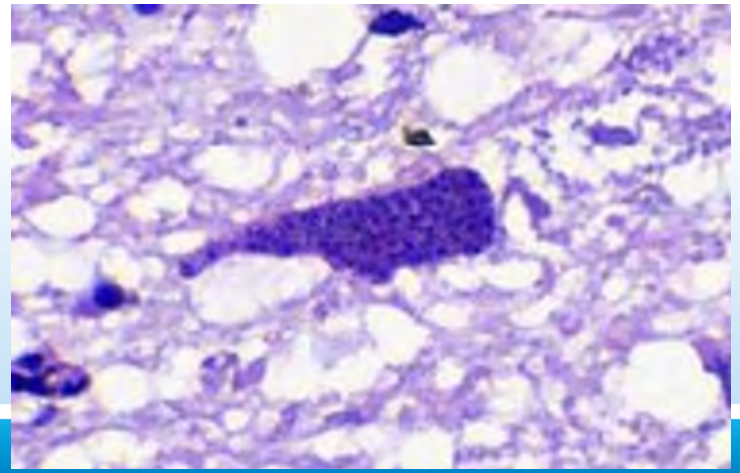


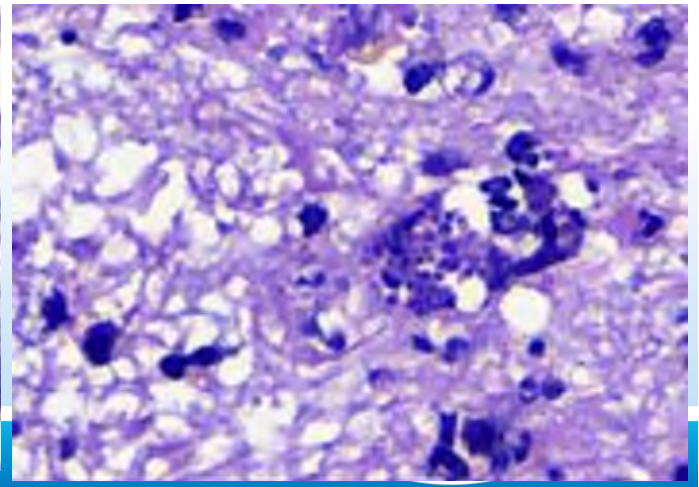


Toxoplasmosis. Chronic, treated, cystic lesions containing macrophages in the periventricular region and cerebellum.

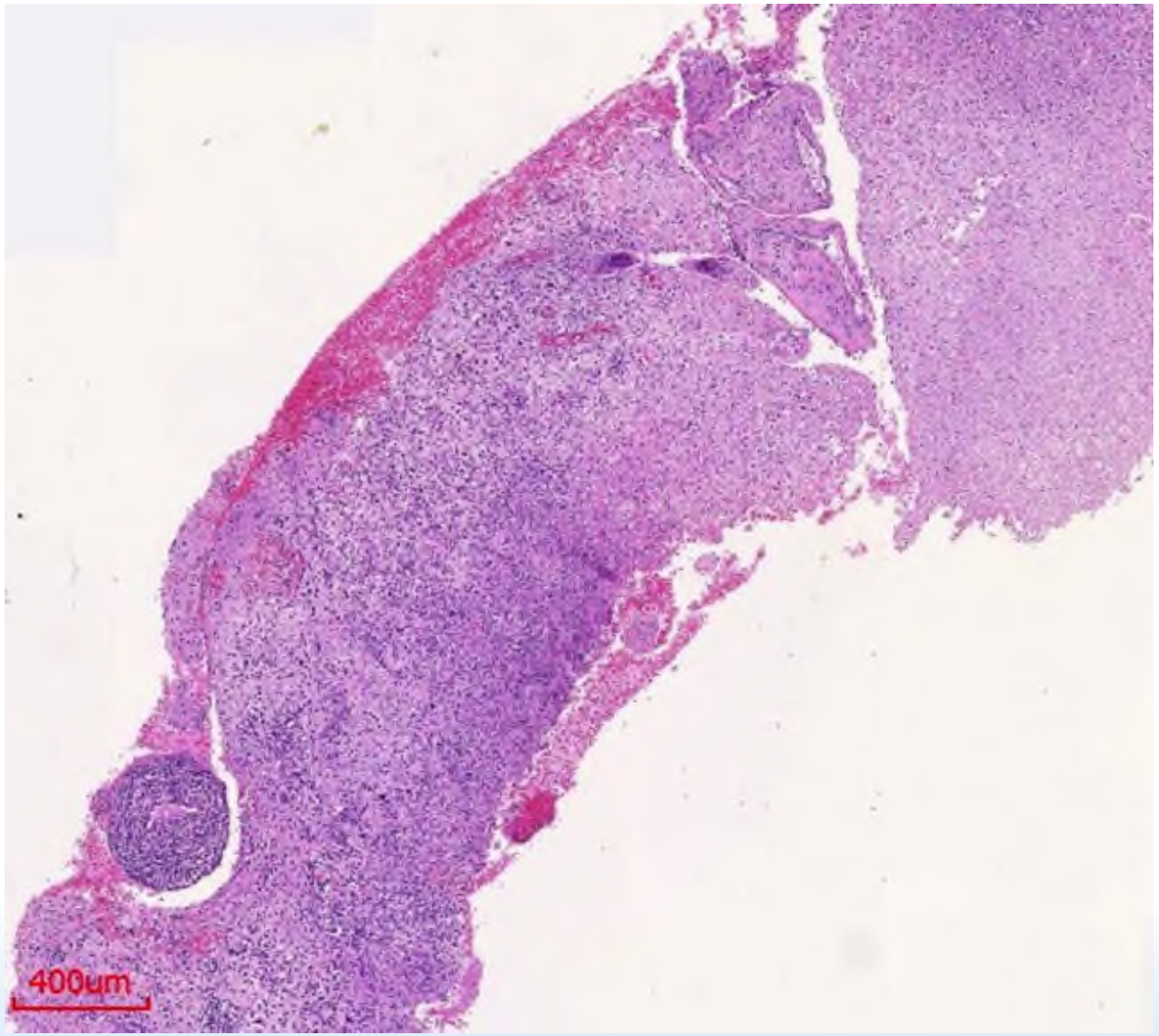


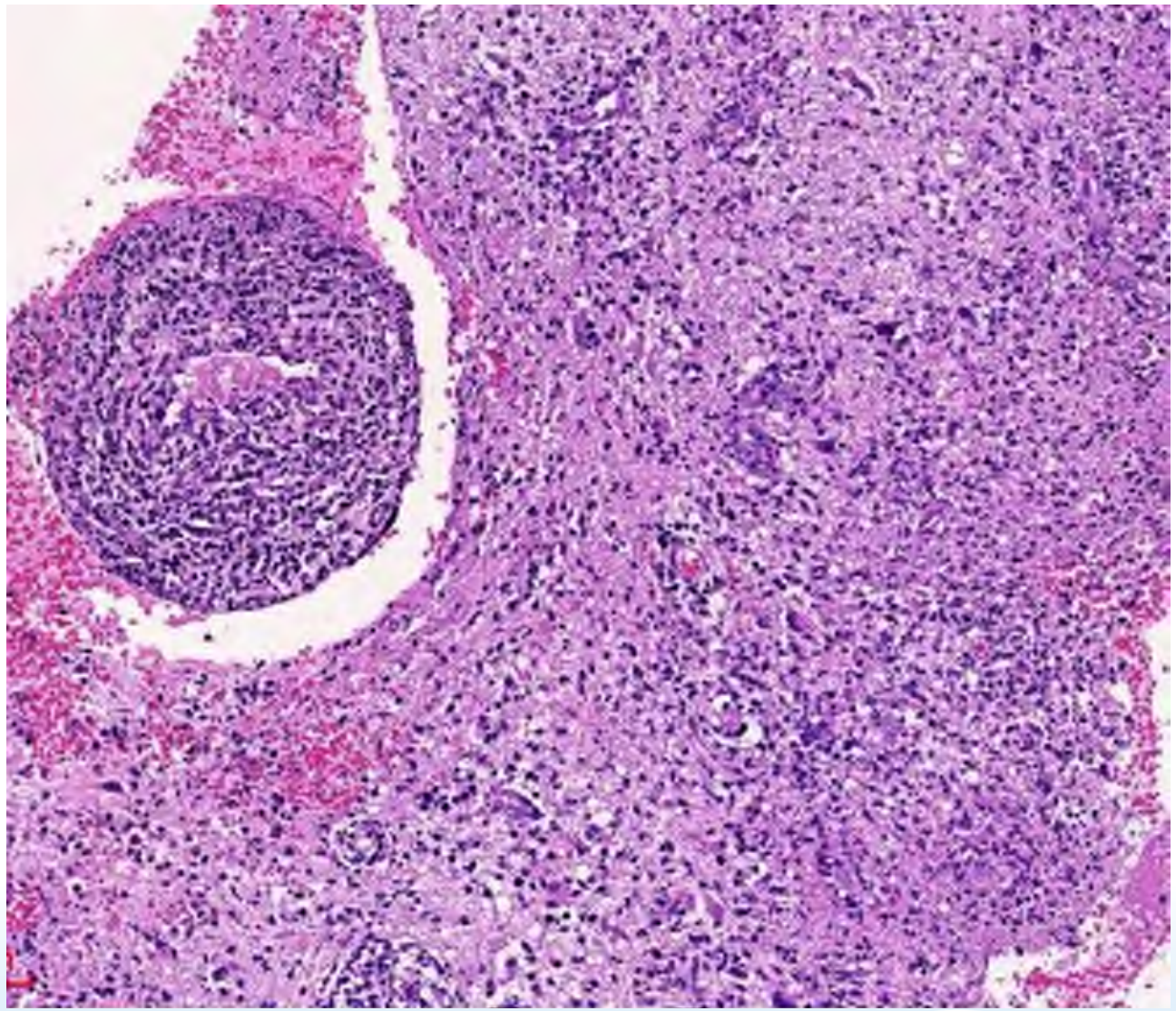




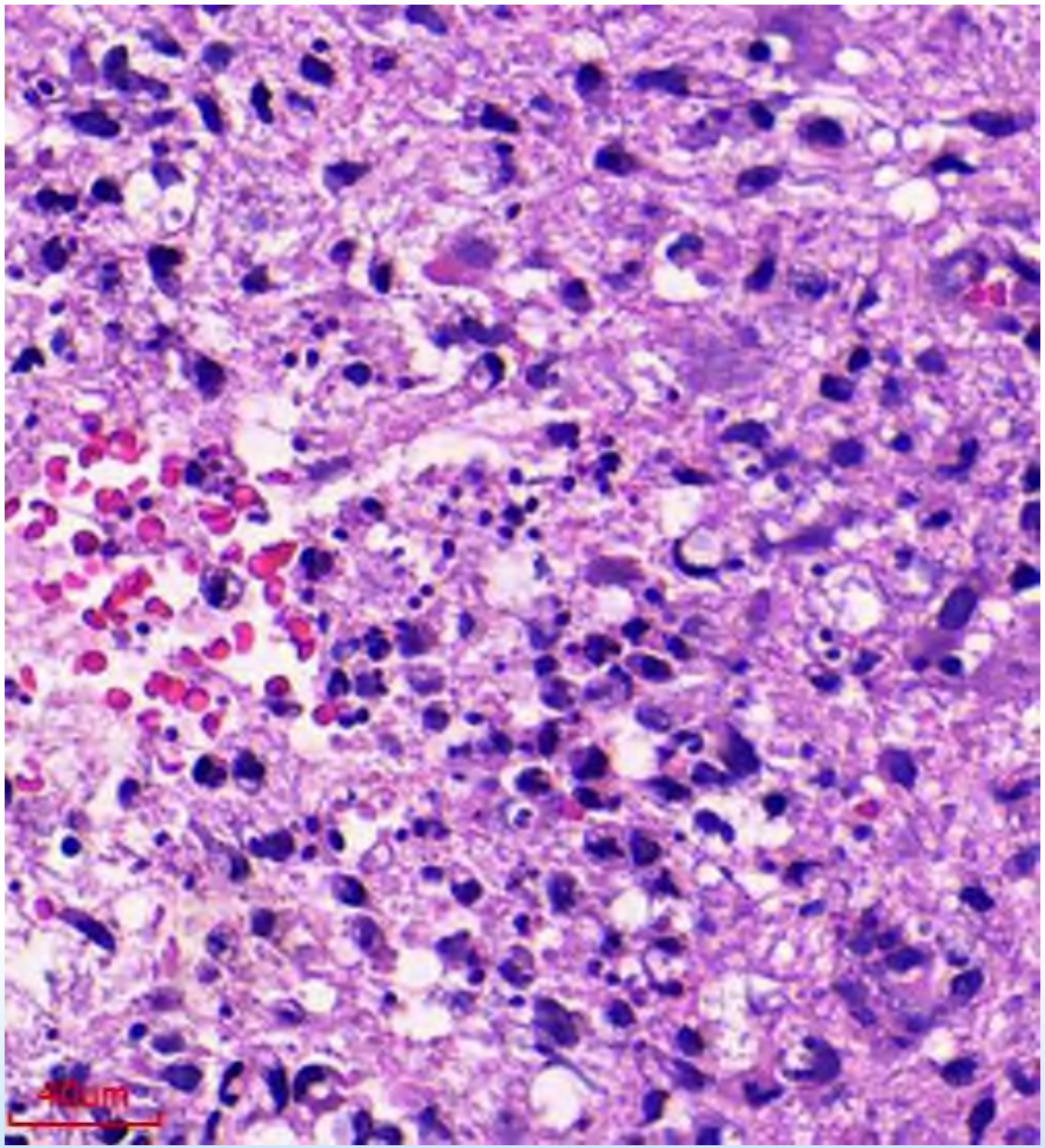


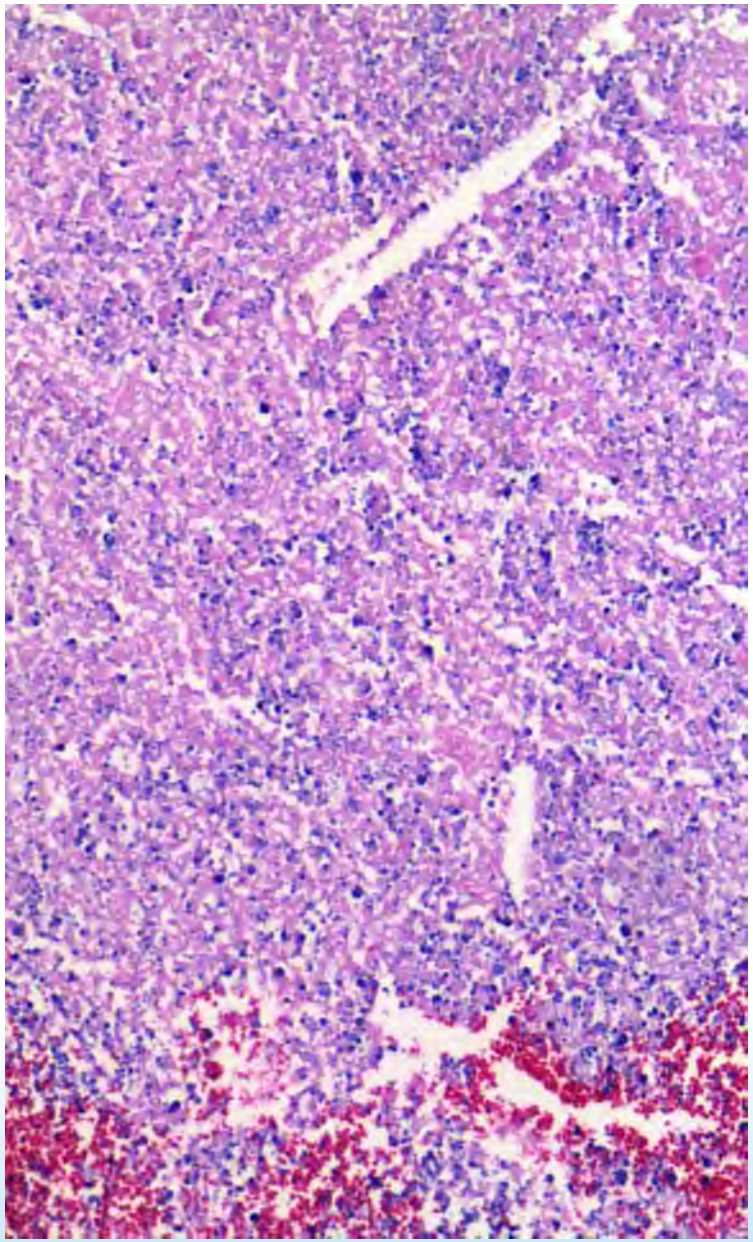
Patient with space occupying lesion operated in 2021
No information about immunodeficiency

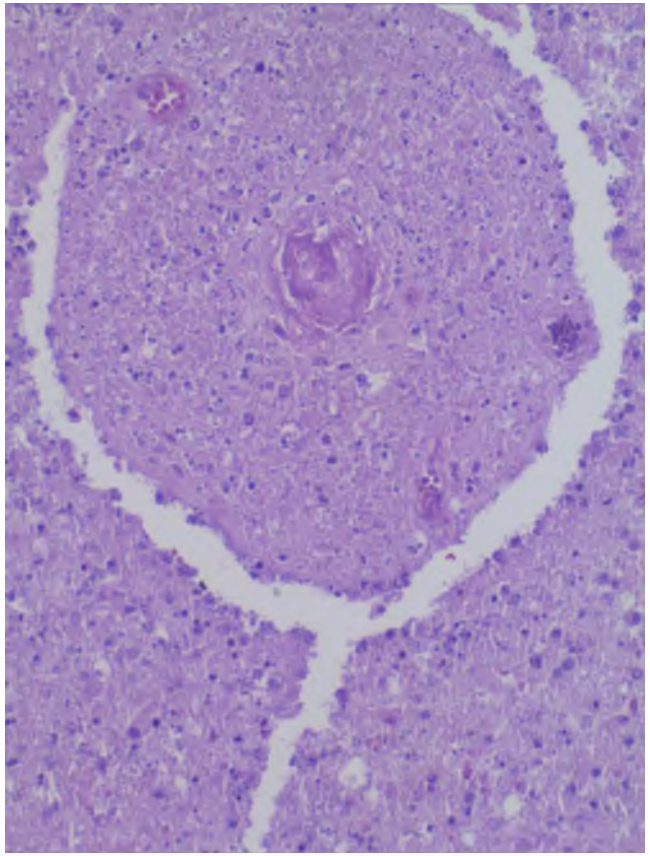




Needle biopsy of space occupying lesion

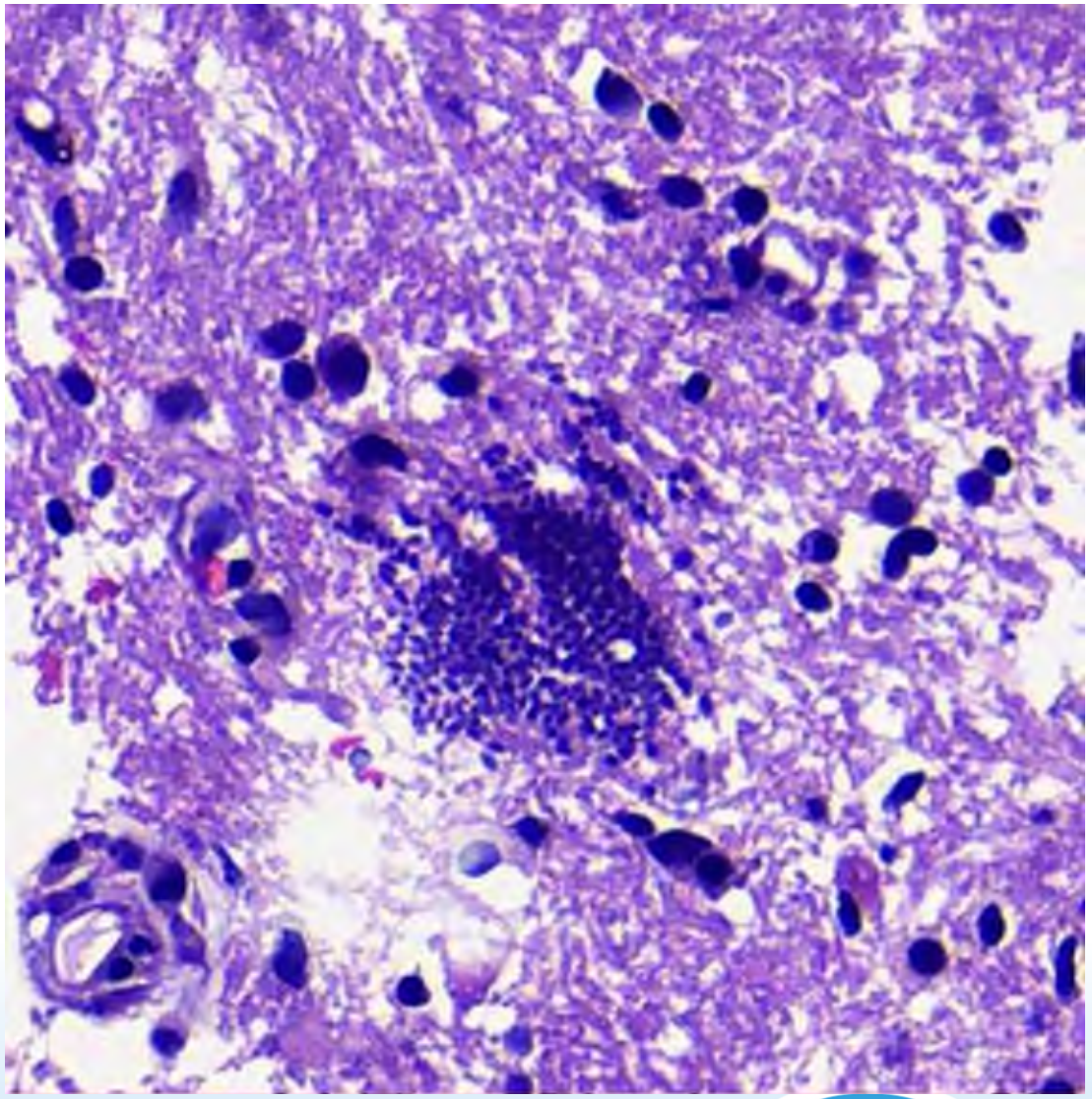




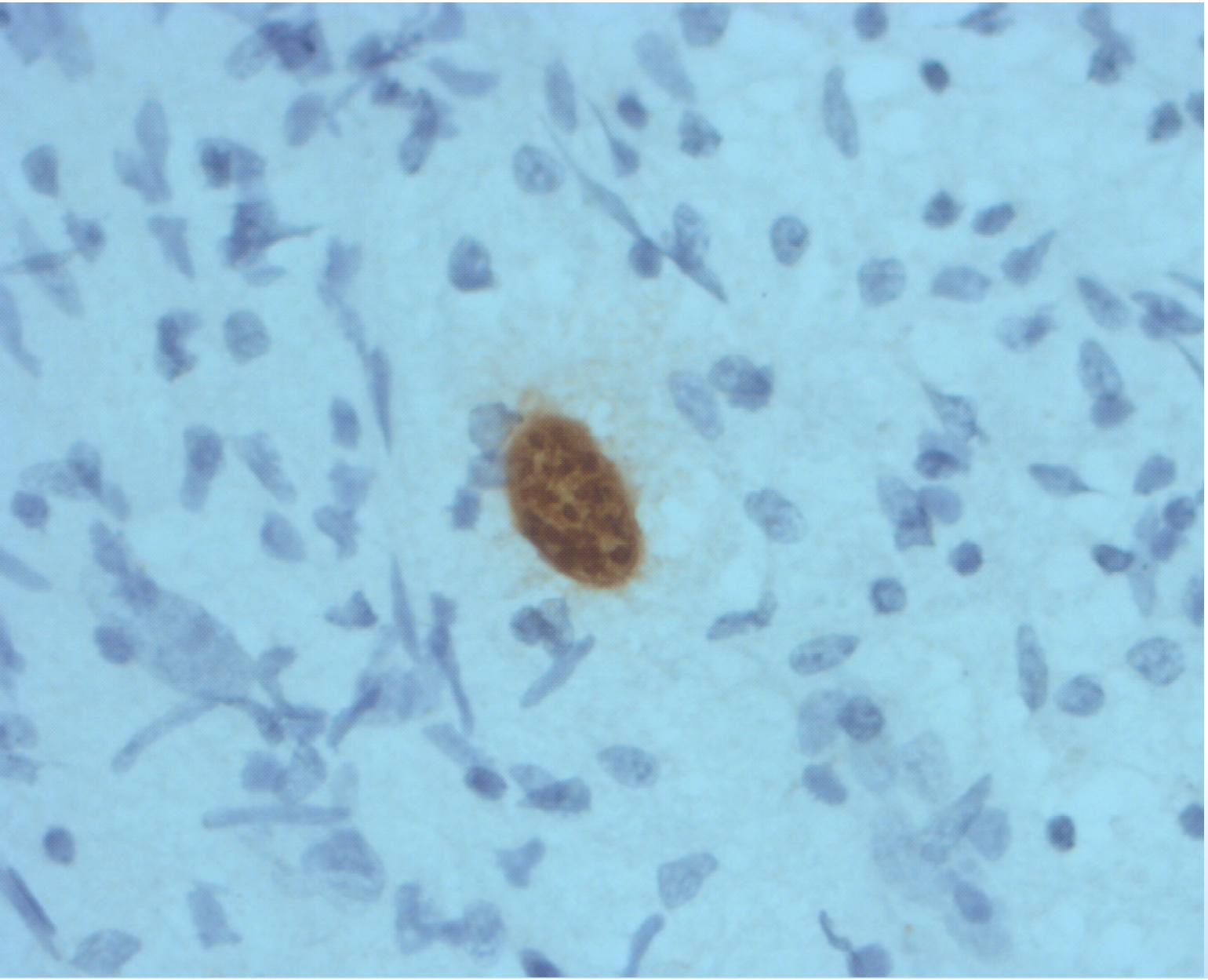


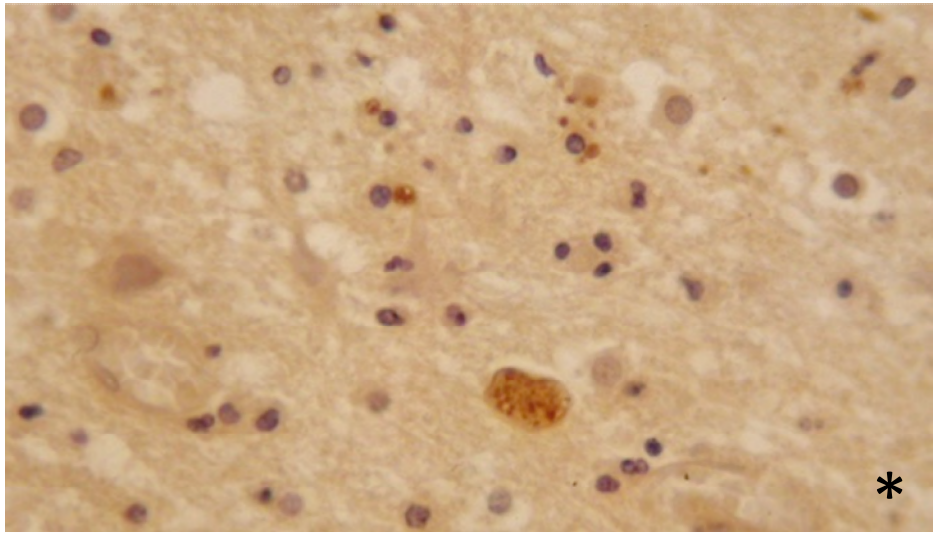
Free forms of T gondii
“Dirty” necrosis and hemorrhage
Vessel necrosis and thrombosis

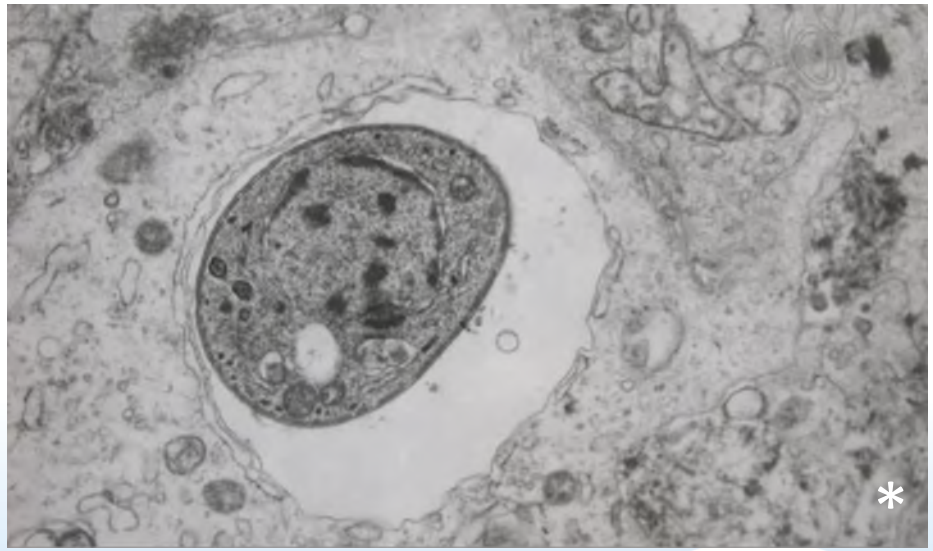
Free forms of Toxoplasma in smear and histological section



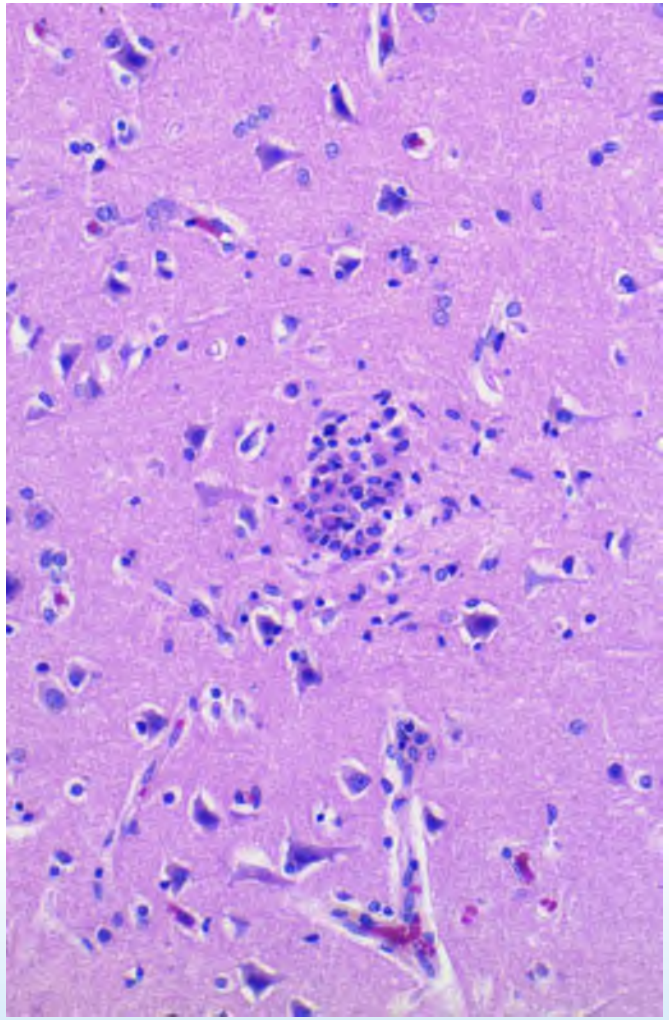
A cyst in a smear and paraffin section immunostained for Toxoplasma and ultrastructural appearance of Toxoplasma

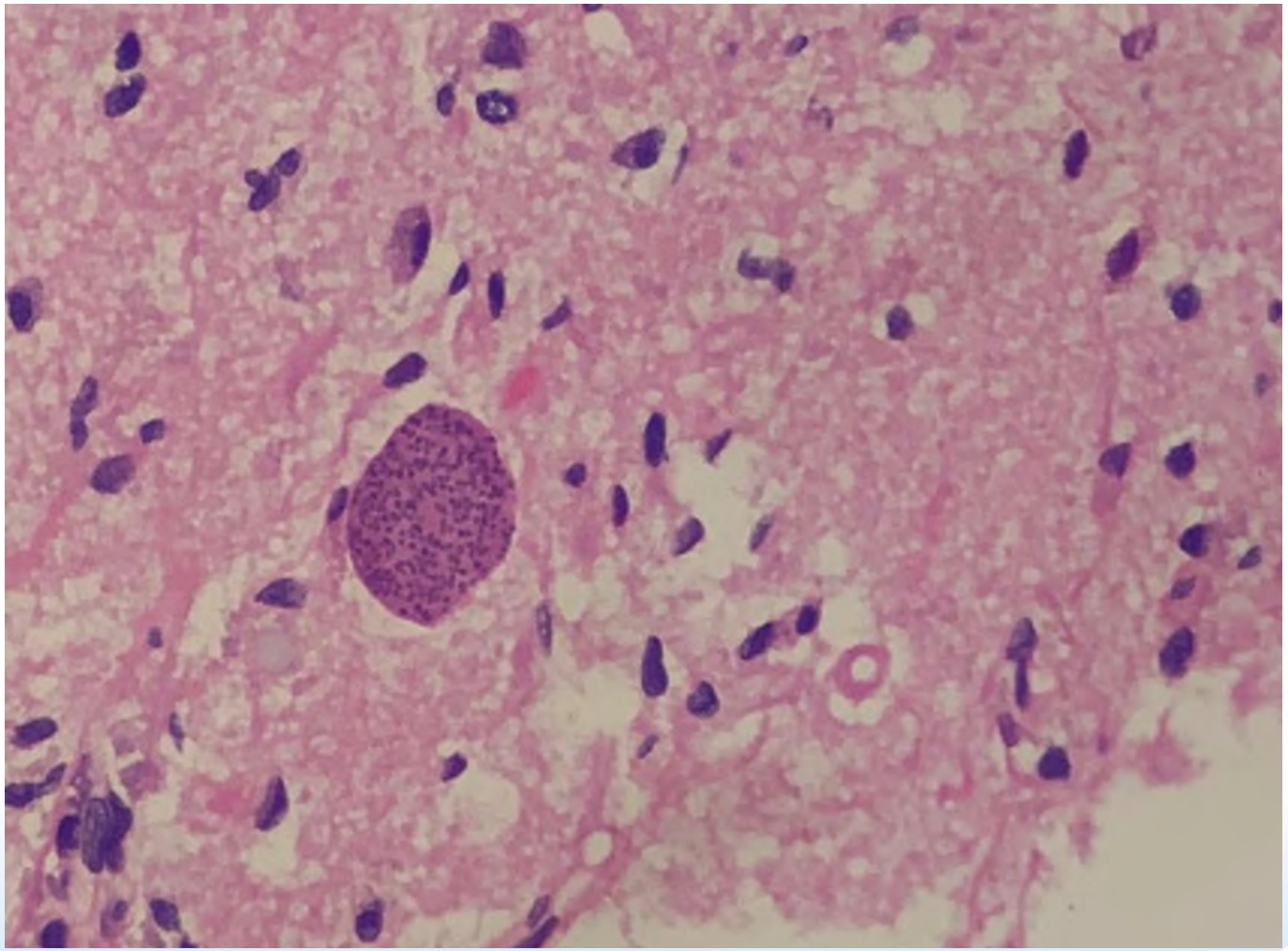






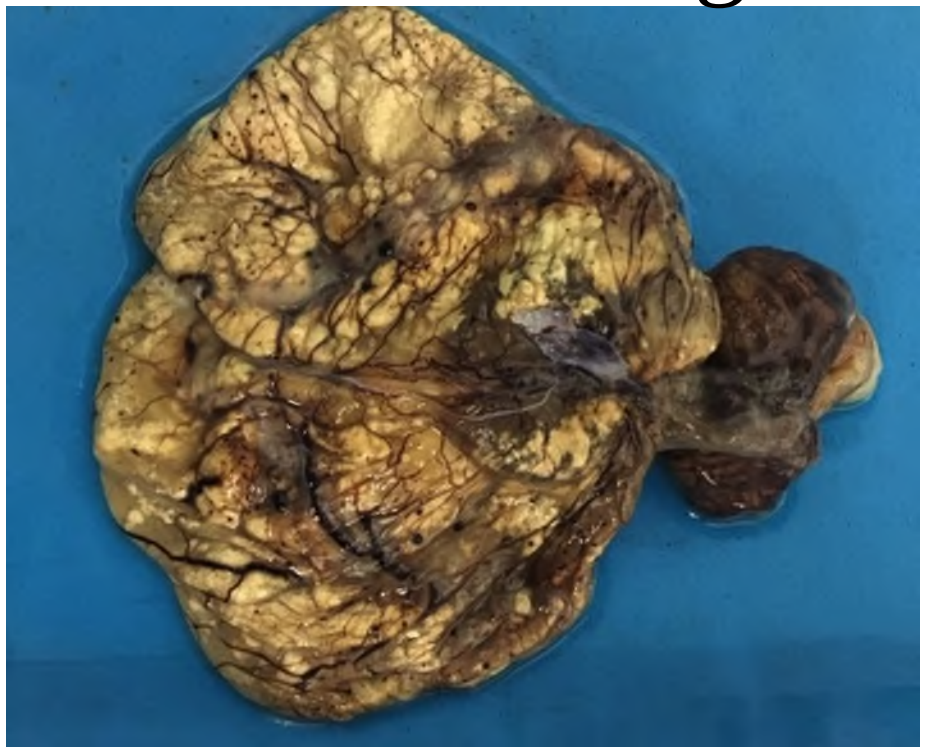
Toxoplasma encephalitis in immunocompromised old patient

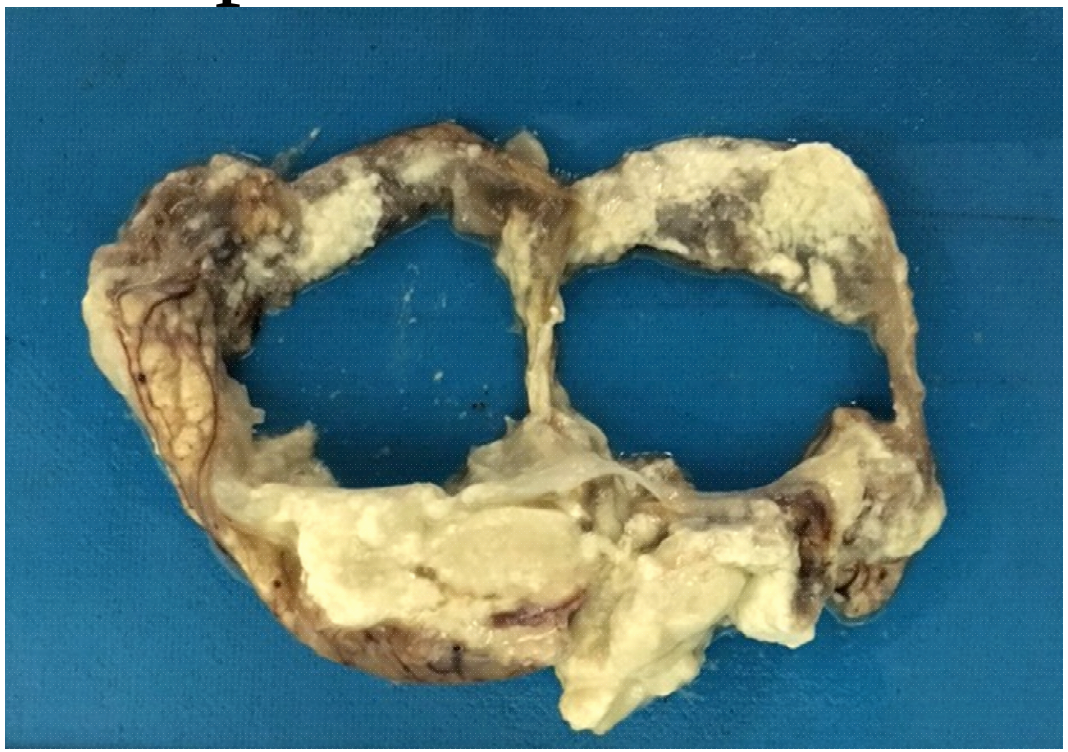


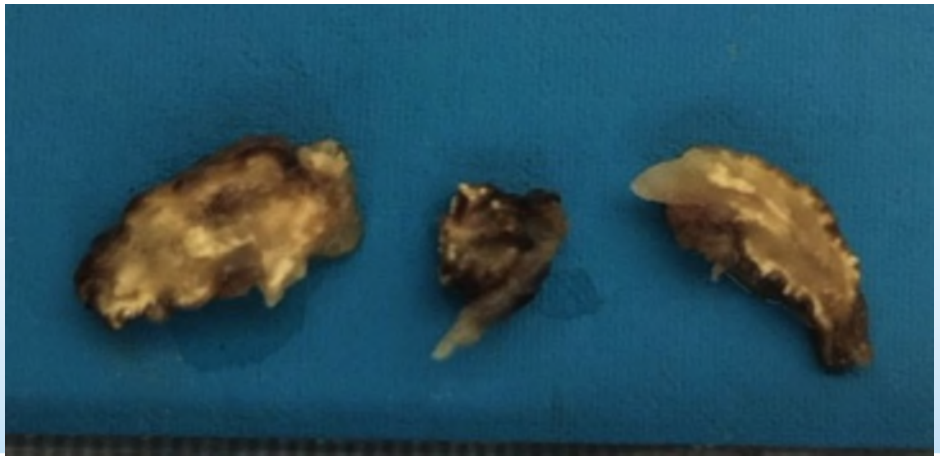


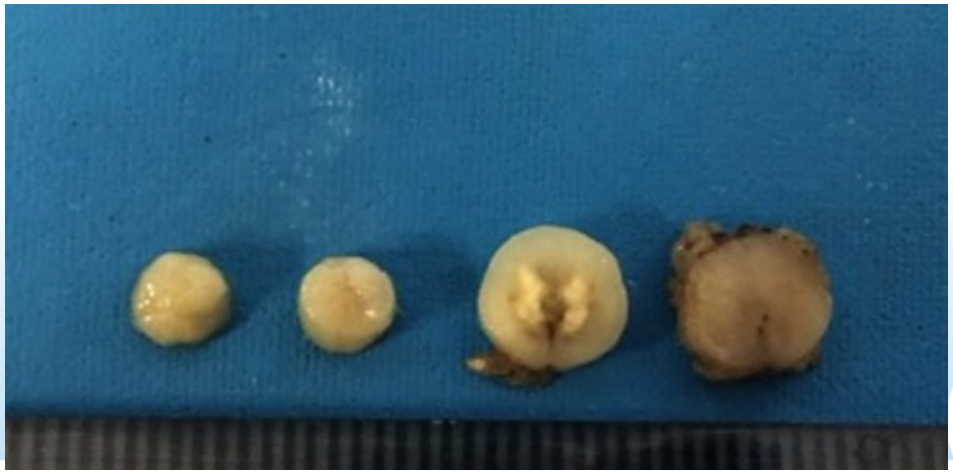
Courtesy of Dr. F Andreiuolo

Congenital Toxoplasmosis

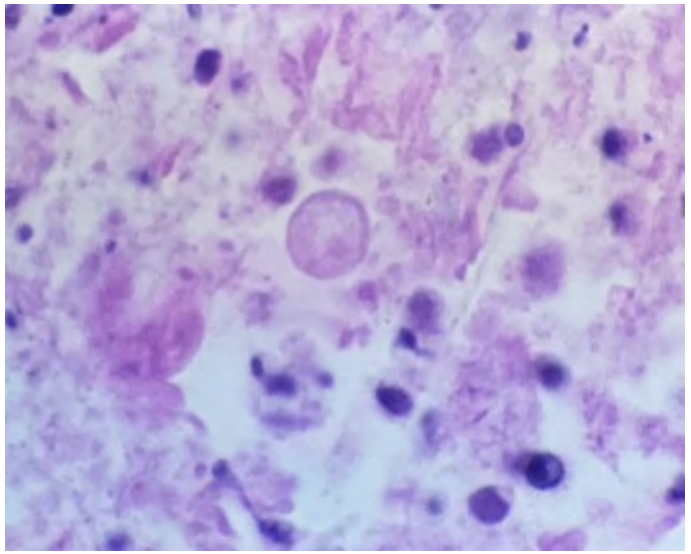




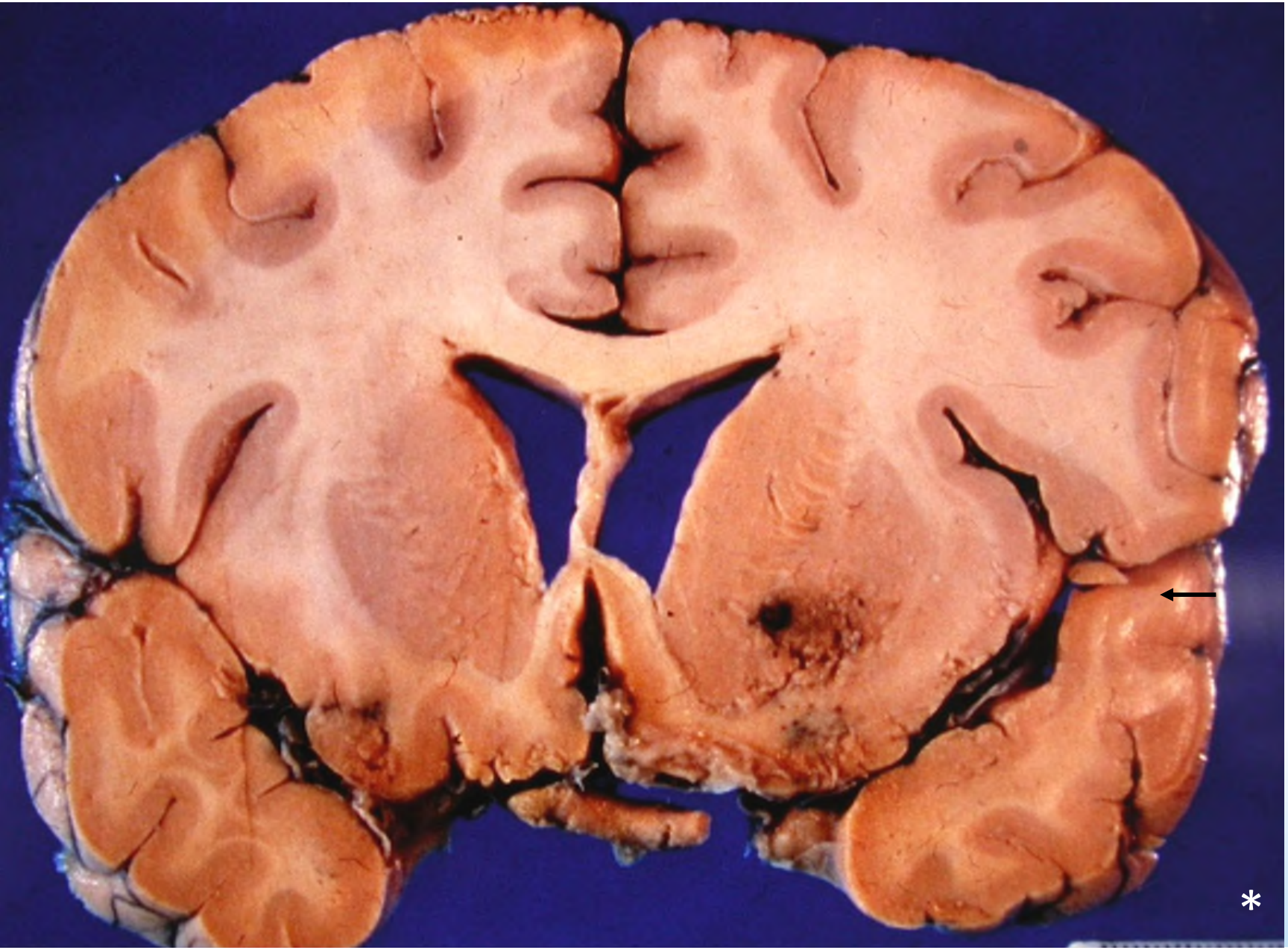


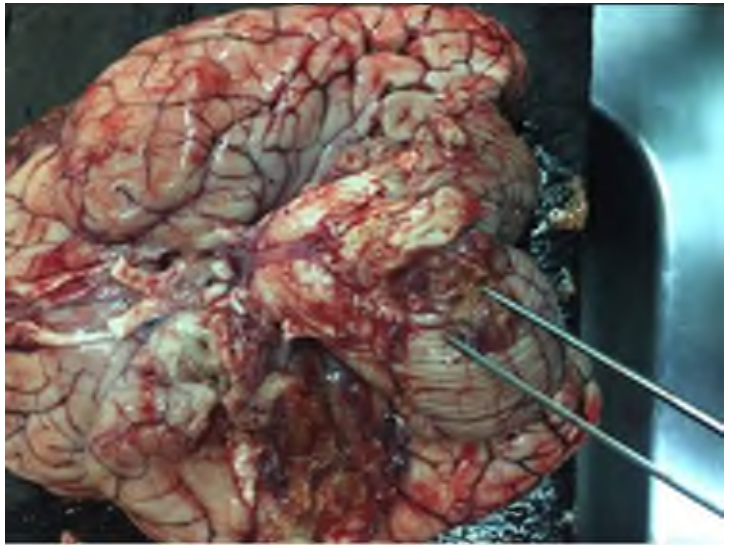


Amebiasis



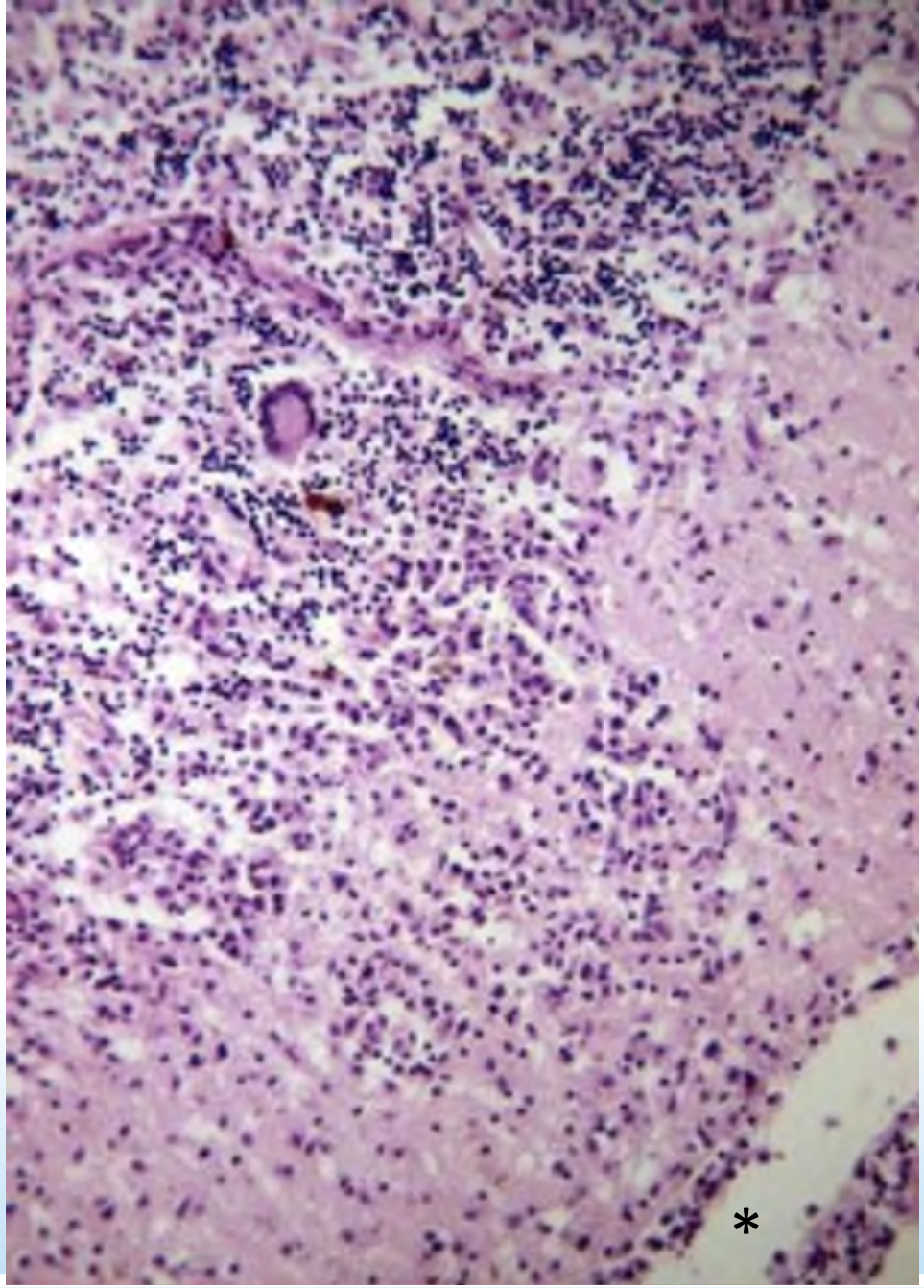
- Entamoeba histolytica (cerebral abscess)
- **Free living amebas**
  - Naegleria fowleri (primary amebic meningoencephalitis)
  - Achantamoeba, Balamuthia mandrilaris (granulomatous amebic encephalitis)
- Cerebral involvement may be fatal

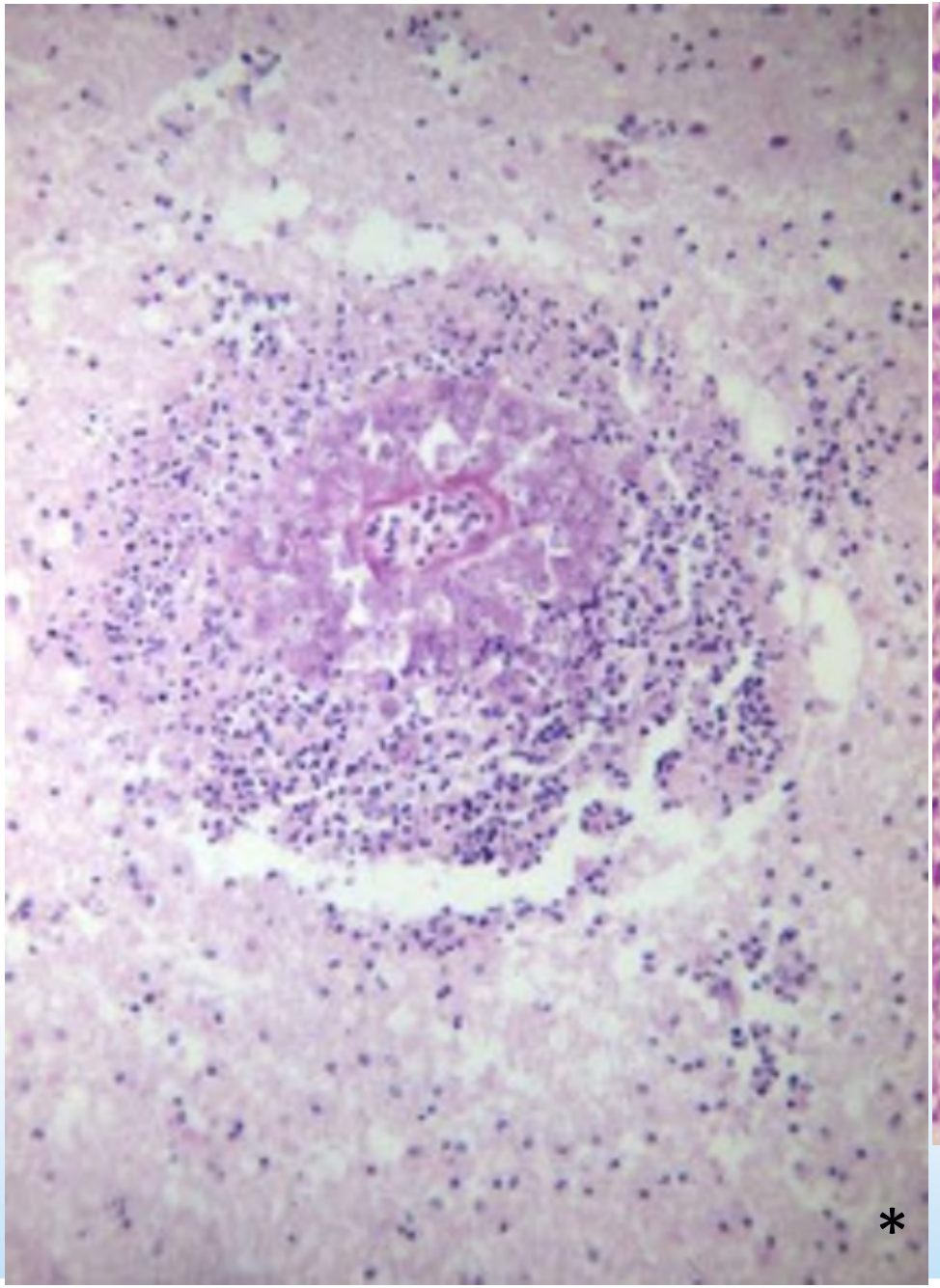


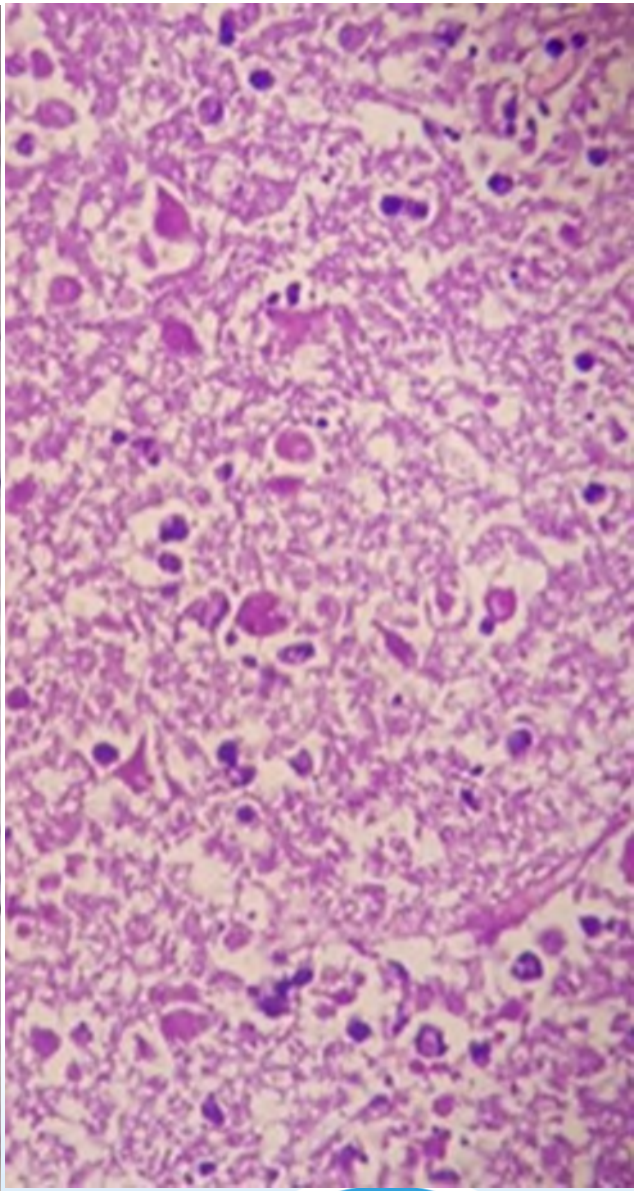


Courtesy of
Dr. C Nogueira

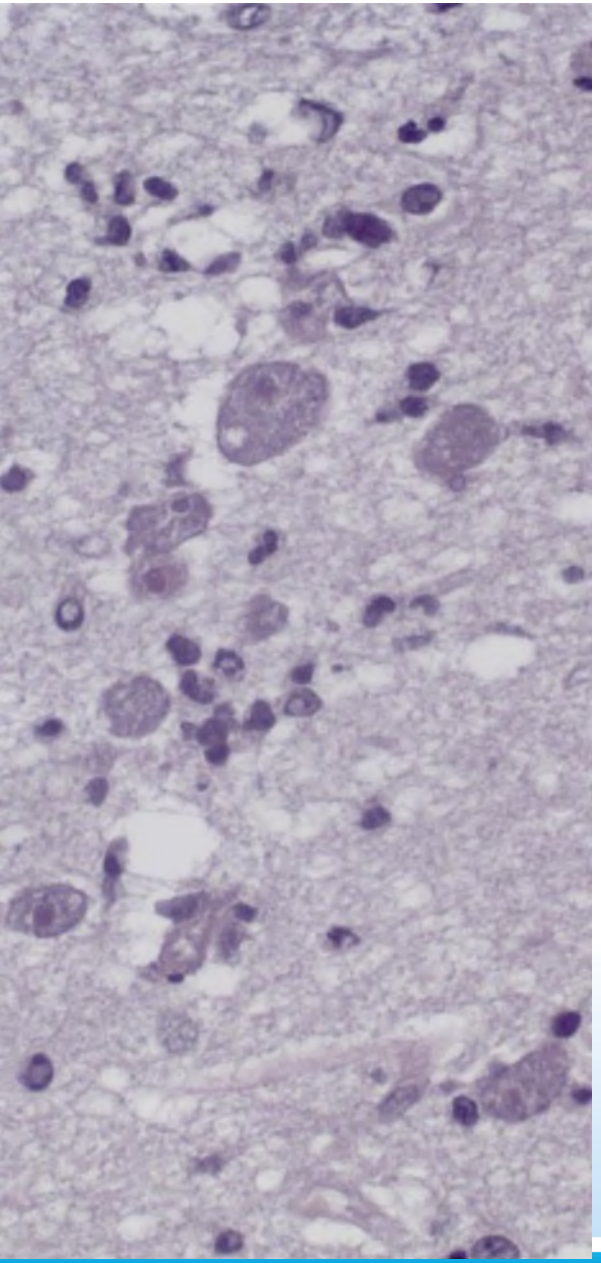
Granulomatous amoebic encephalitis. Foci of haemorrhagic softening.



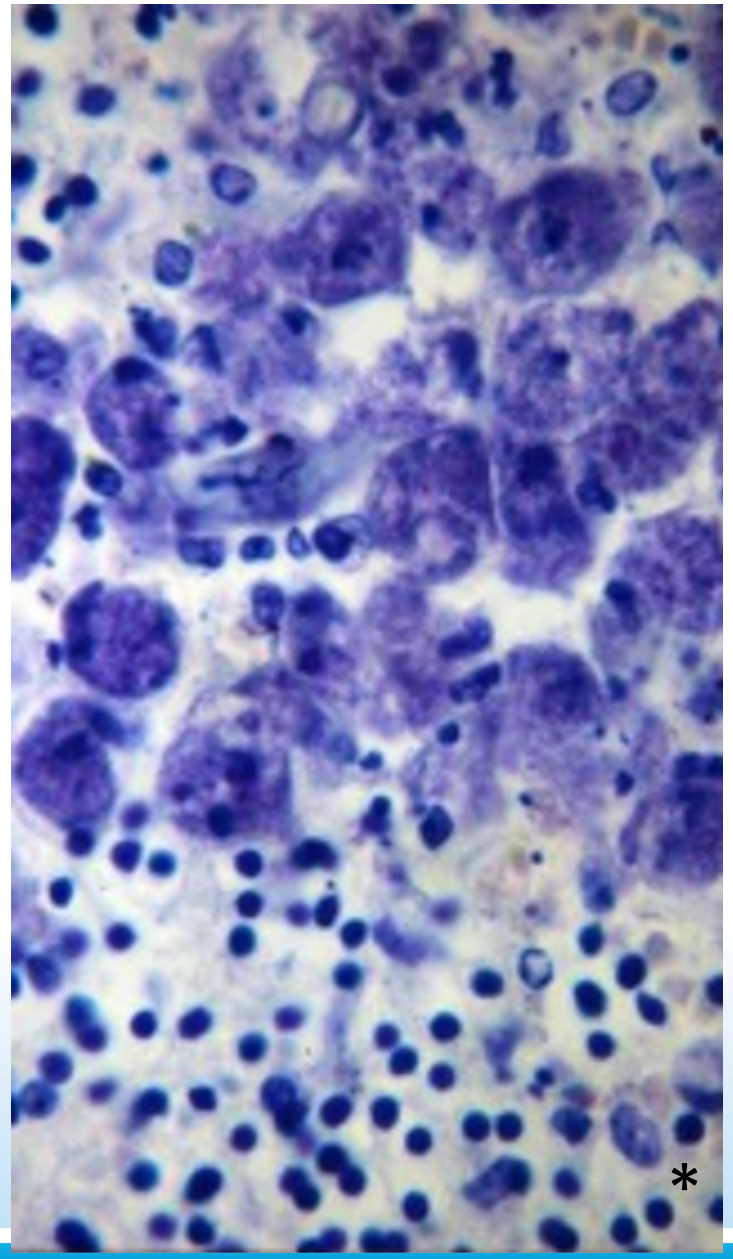




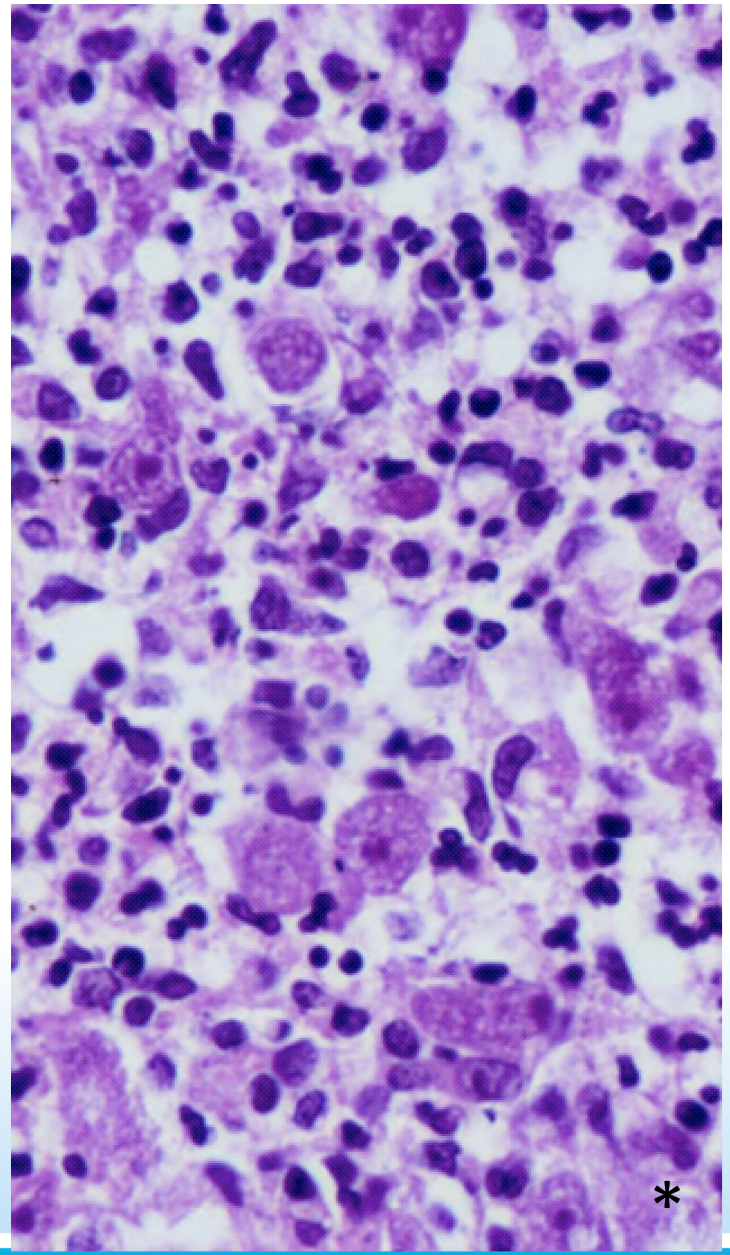
H&E



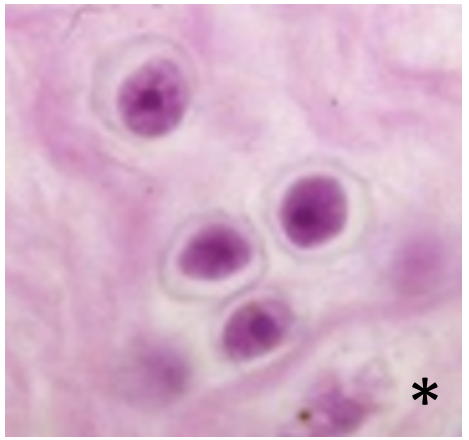
Giemsa

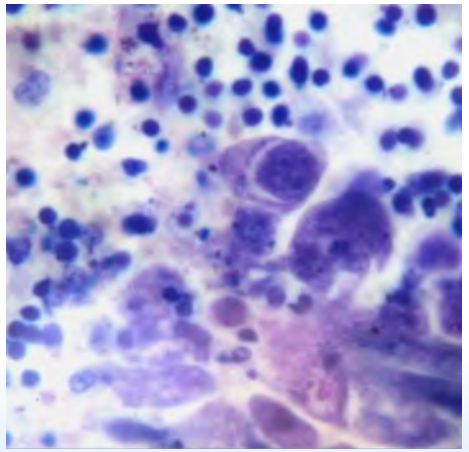


PAS



Cystic forms



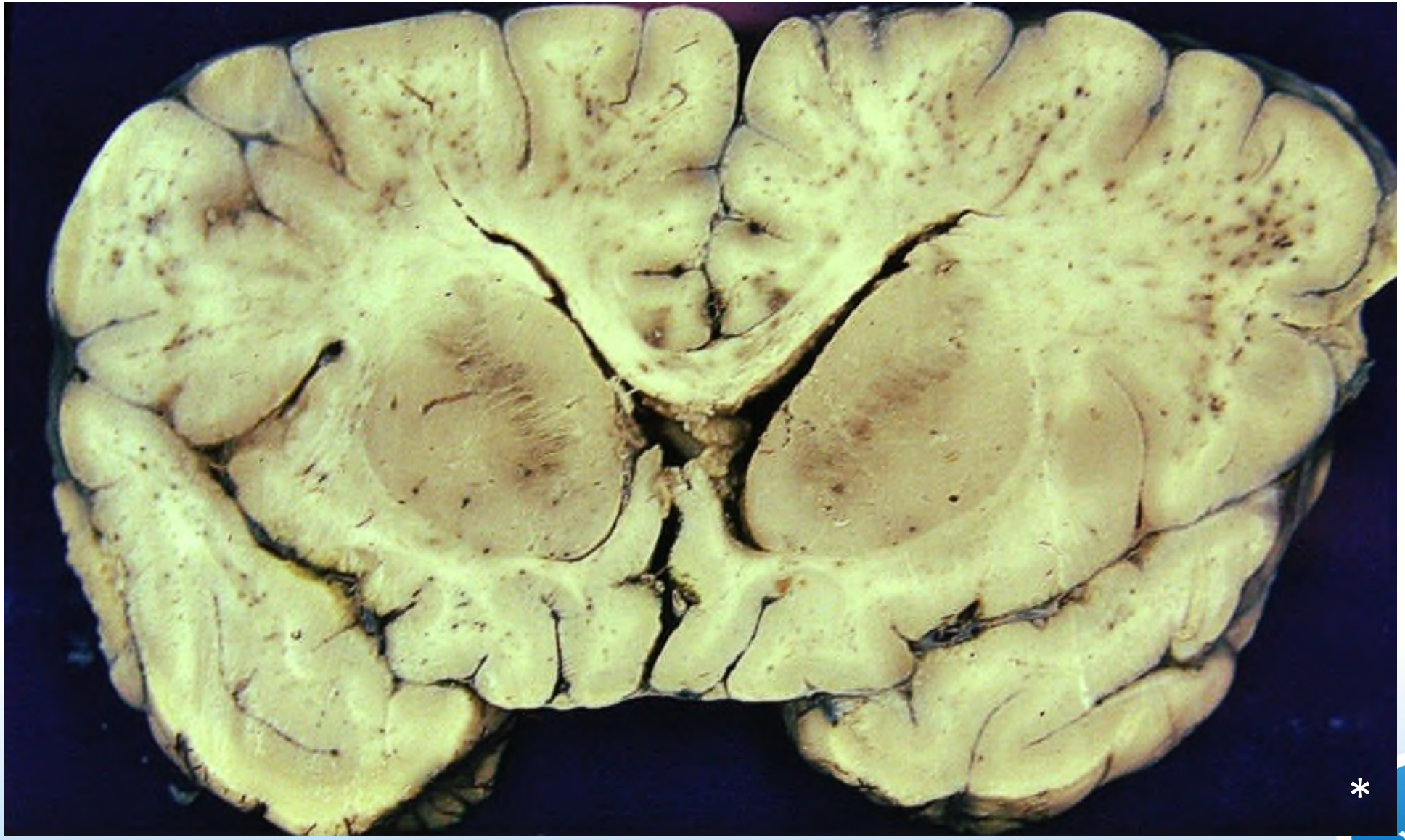


Cerebral Malaria (occurs in the severe form of infection)

- Plasmodium falciparum
- Acquired by the bite of an infected Anopheles mosquito
- Major health care problem in many regions of the tropics and sub-tropics
- Infants and children are particularly affected
- Rapidly progressive encephalopathy with various degrees of consciousness loss and fits.
- Neuropathology helped understanding the pathogenesis


AM
RJ

MALARIA



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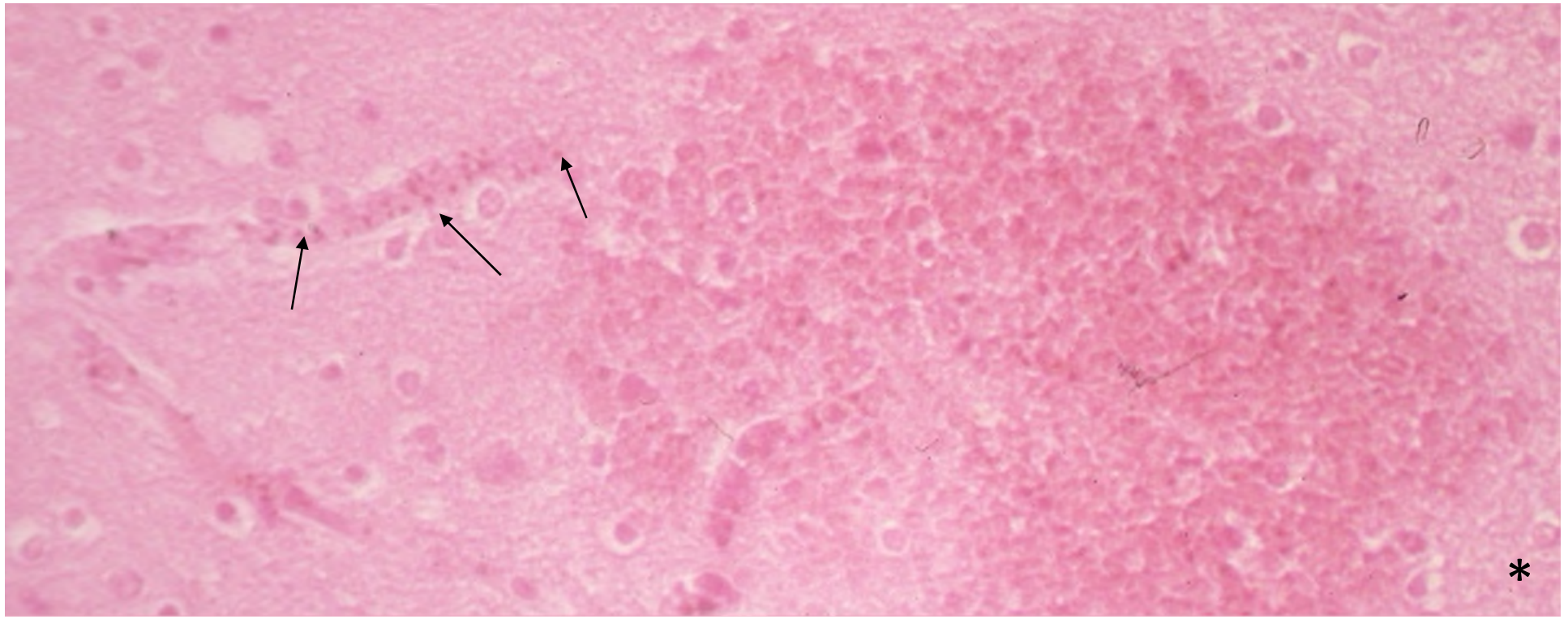


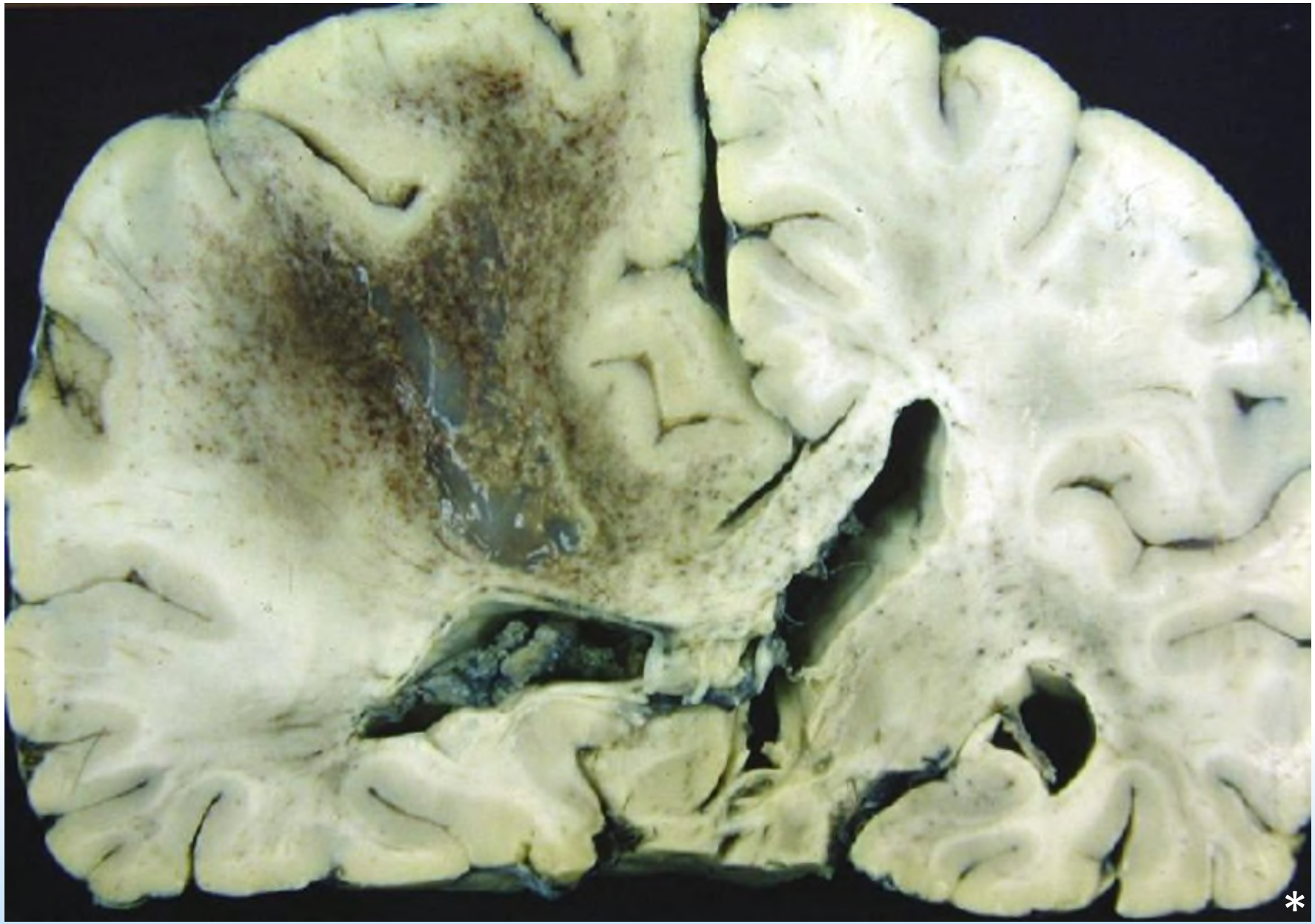
Haemozoin pigment deposition in the lining of the blood vessels (arrows) may obscure the parasites in the trophozoite stage

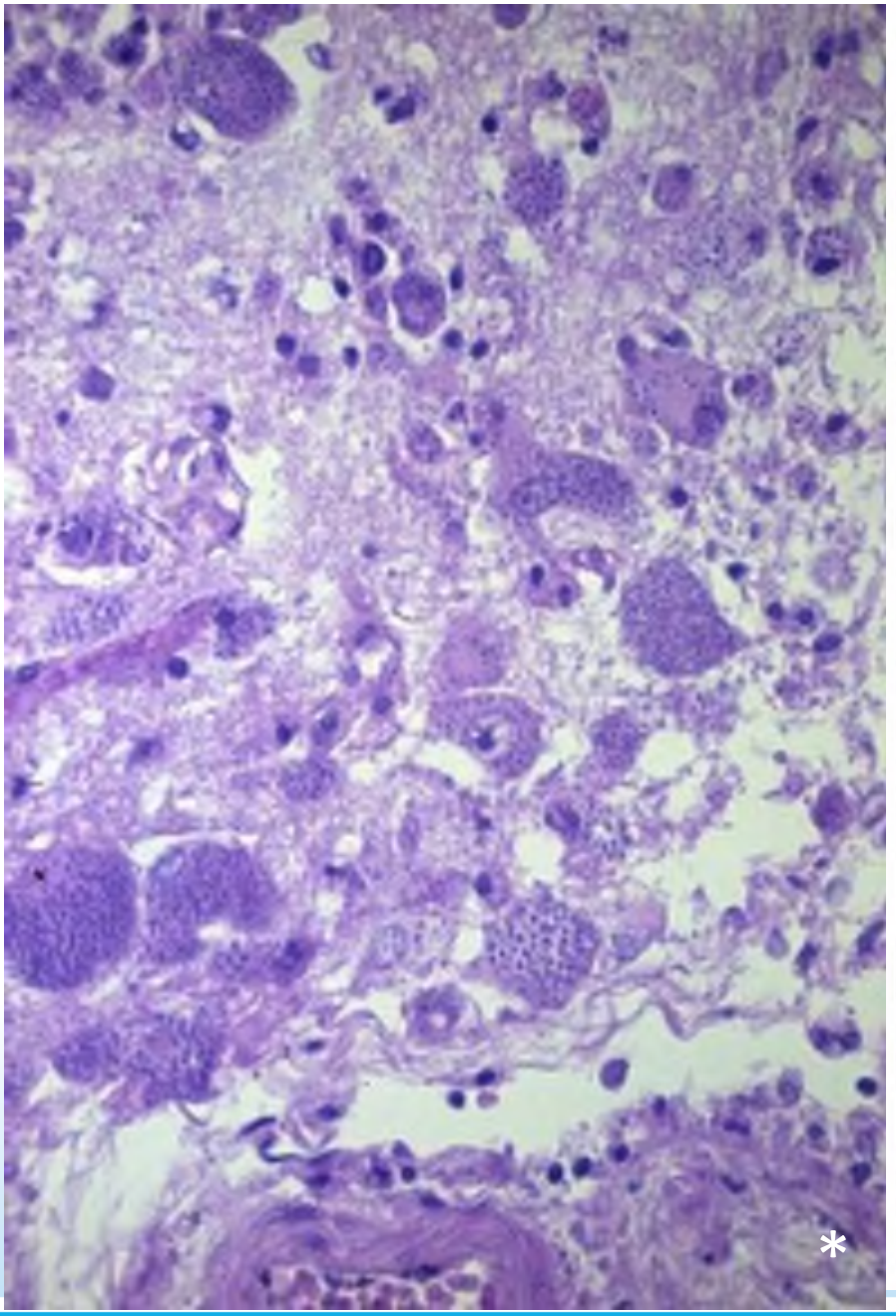
Trypanosomiasis

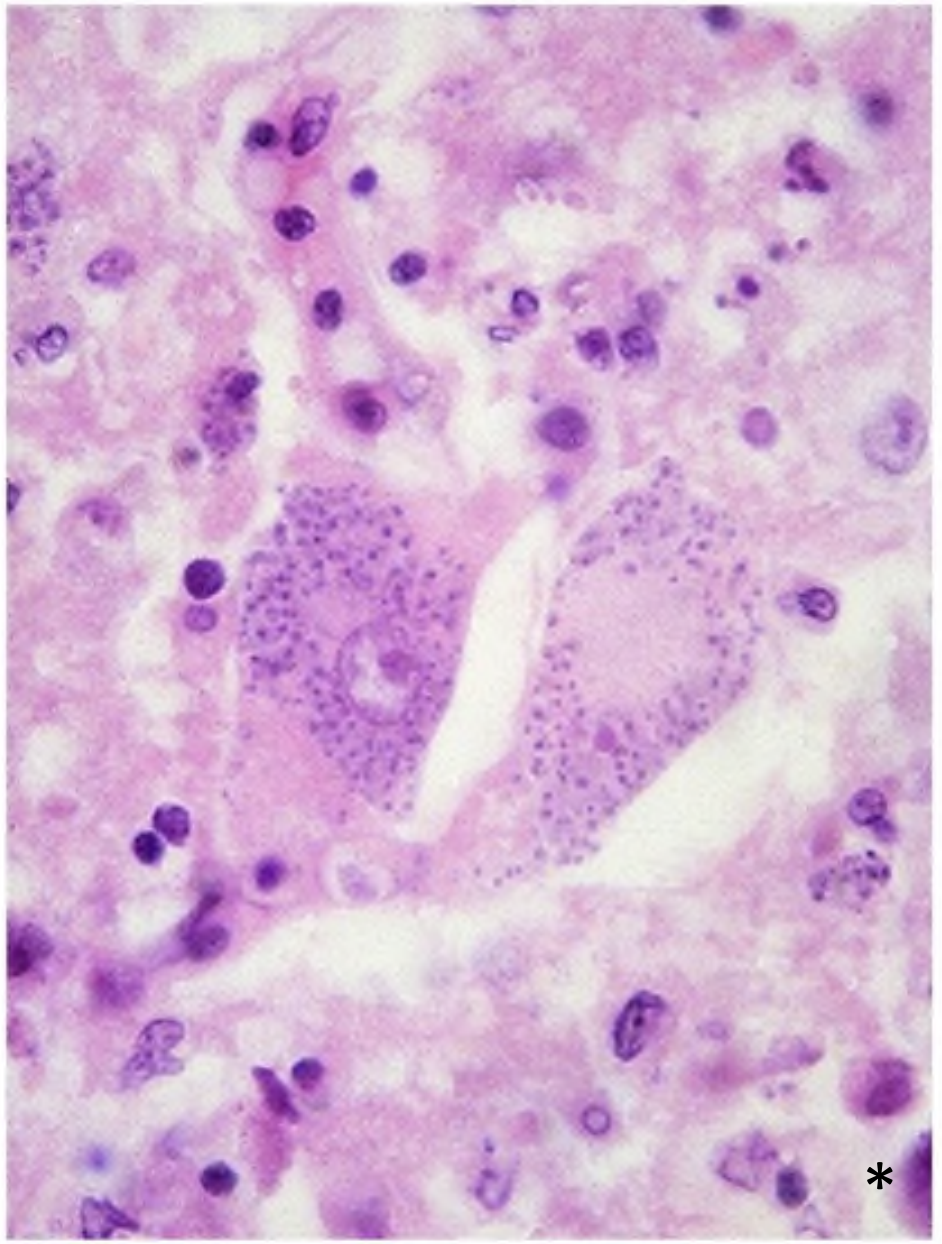
- African (Sleeping sickness)
  - T brucei rhodesiense (east and central Africa) and gambiense (western and sub-Saharan regions)
  - Transmitted by tsetse fly
  - Sub-acute and chronic meningoencephalitis
- American (Chagas' disease)
  - T cruzi, transmitted by reduviid buds
  - Endemic in South America especially Brazil
  - Autonomic system is particularly affected (megaviscera)
  - CNS involvement uncommon except in reactivated forms

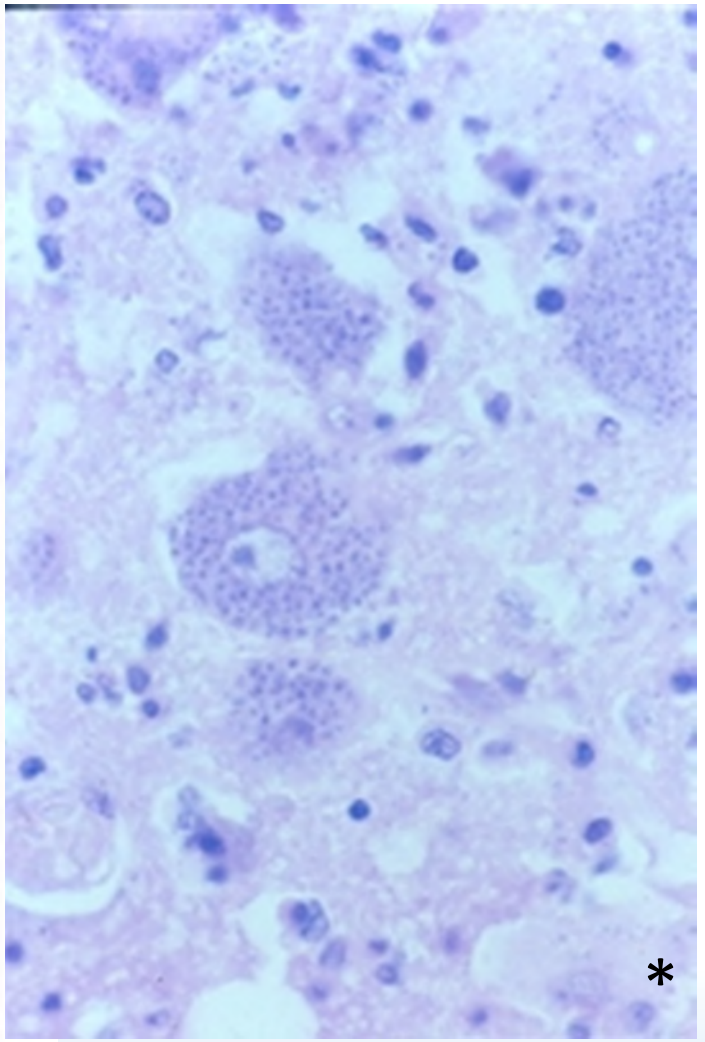
Reactivated disease

- Appeared in endemic areas due to increase in number of immunosuppressed patients
- Extensively necrotic lesions and intense parasitism

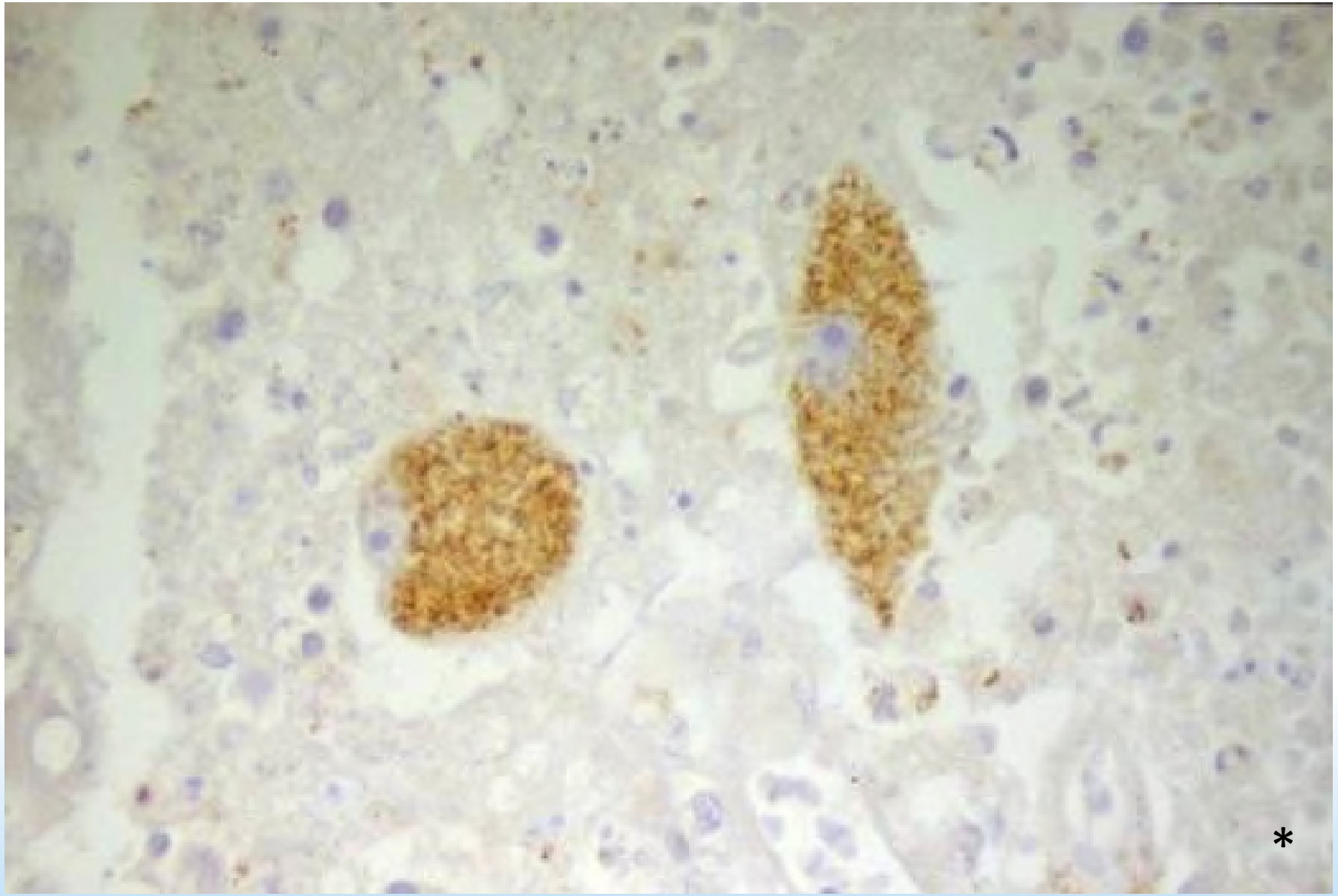








Immunostaining for T cruzi



Etiology

Bacterial: Pyogenic (Gram + / -), Tuberculosis, Syphilis

Fungal: Cryptococcosis, Histoplasmosis, Mucormycosis, Aspergillosis, Paracoccidioidomycosis

Parasitic: Protozoa: Toxoplasmosis, Trypanosomiases, Malaria, Amebiasis

Helminths: Cestodes: Cysticercosis, Hydatidosis

Nematodes: Strongyloidiasis

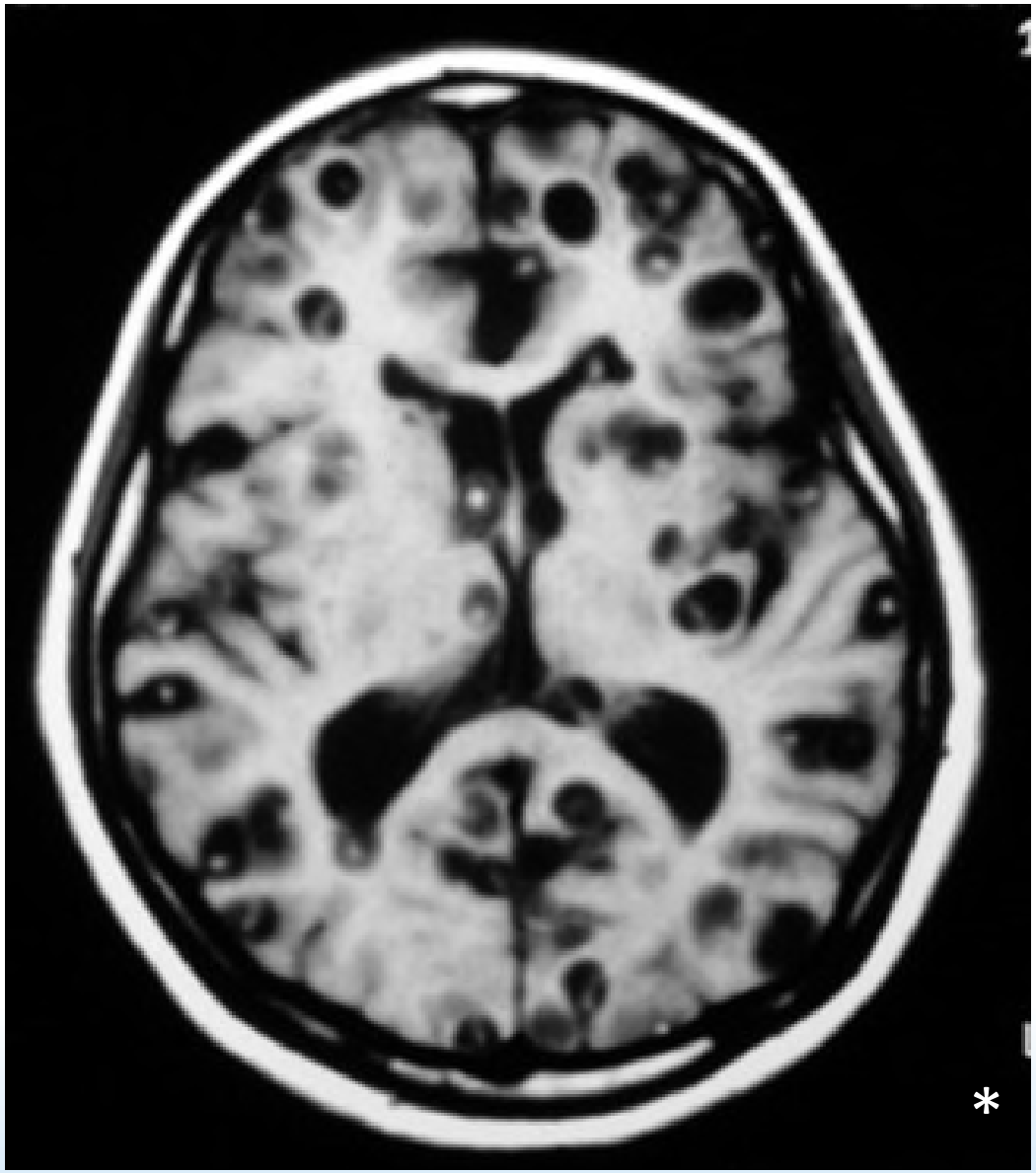
Trematodes: Schistosomiasis

Viral: Arboviroses (Dengue, Zika), Herpes, CMV, HIV, HTLV1, Measles, Poliomyelitis, PML, Rabies.

Neurocysticercosis

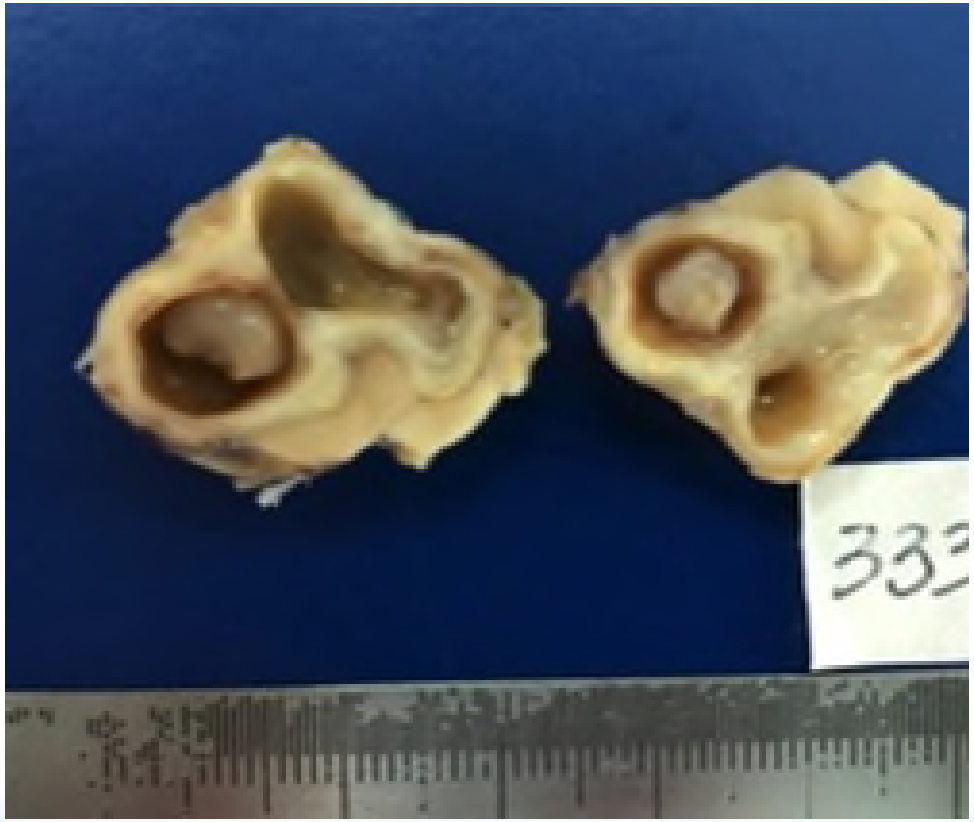
- Cysticercus cellulosae, the larval form of Taenia solium.
- Usually found in pork (the intermediate host)
- Humans are intermediate hosts after ingesting the ova of T. solium (usually in vegetables).
- Ova develop into larvae that penetrate intestinal wall, invade lymphatic and veins, disseminate to skeletal muscle and CNS.
- Clinical features depend on number and location of the cysts


MG
SP

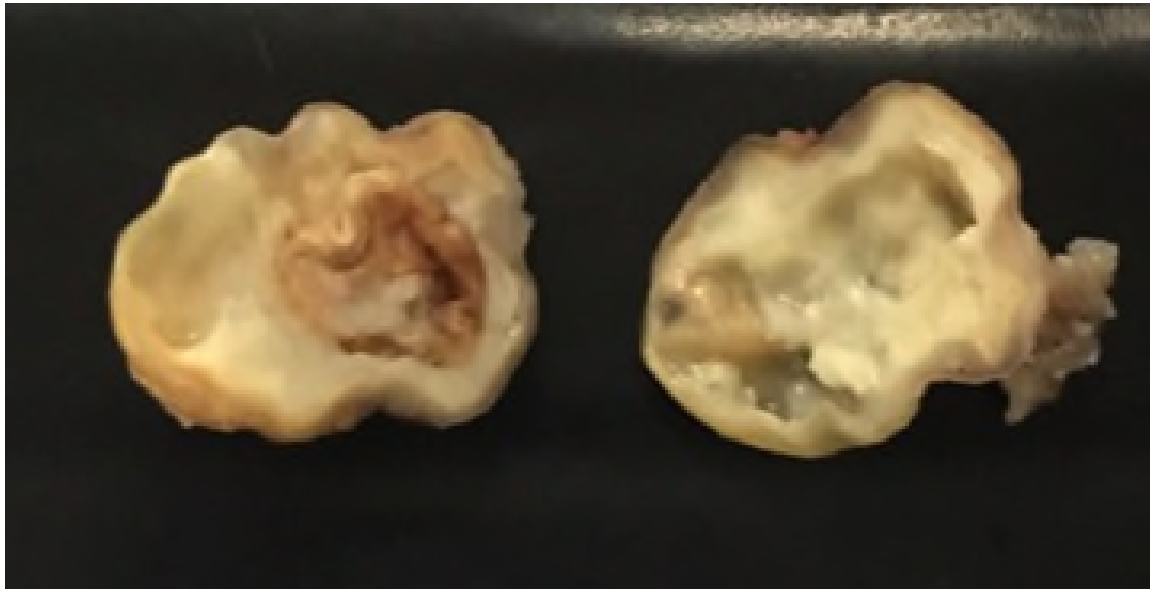


Neurocysticercosis – surgical specimens

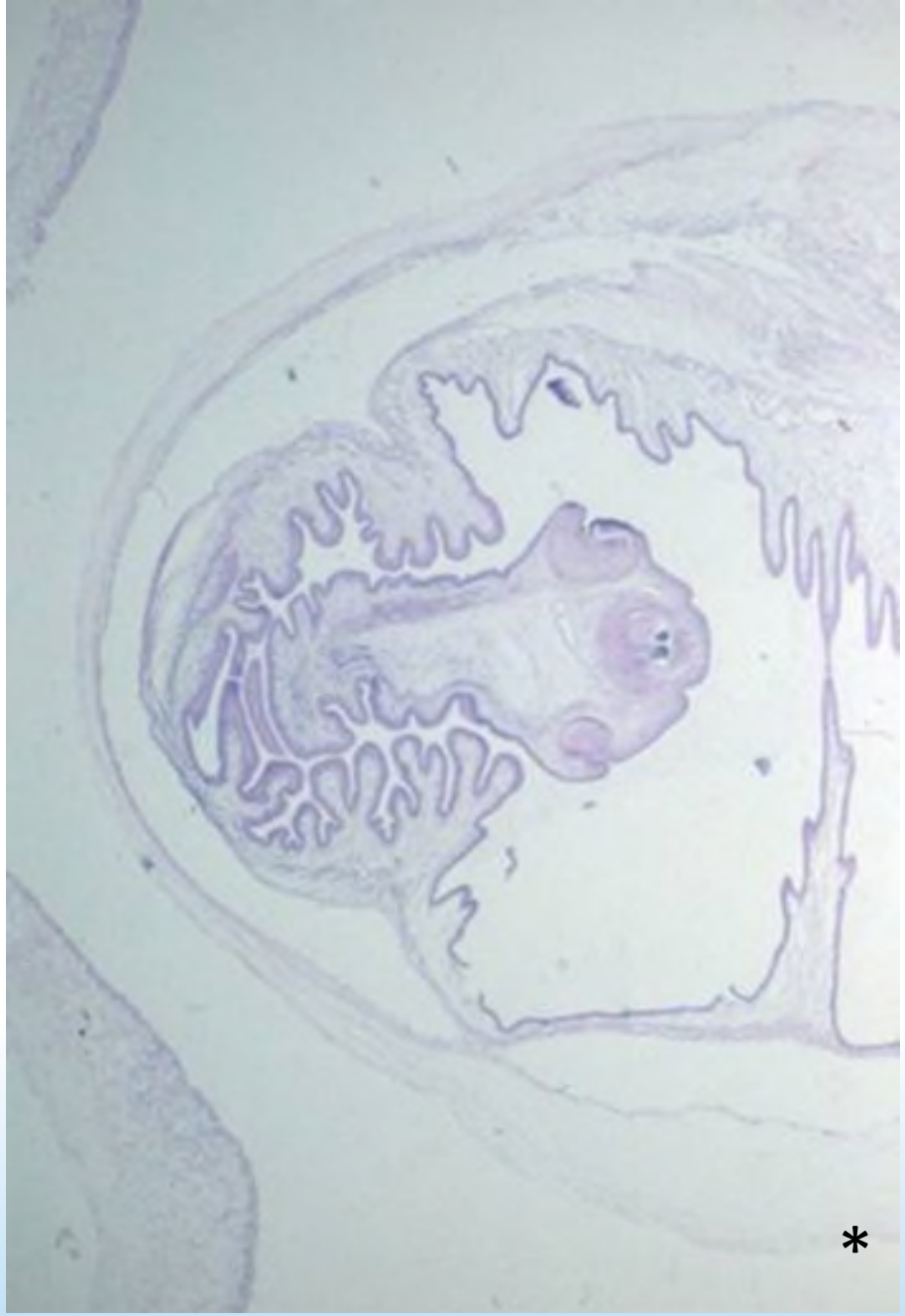
scolex

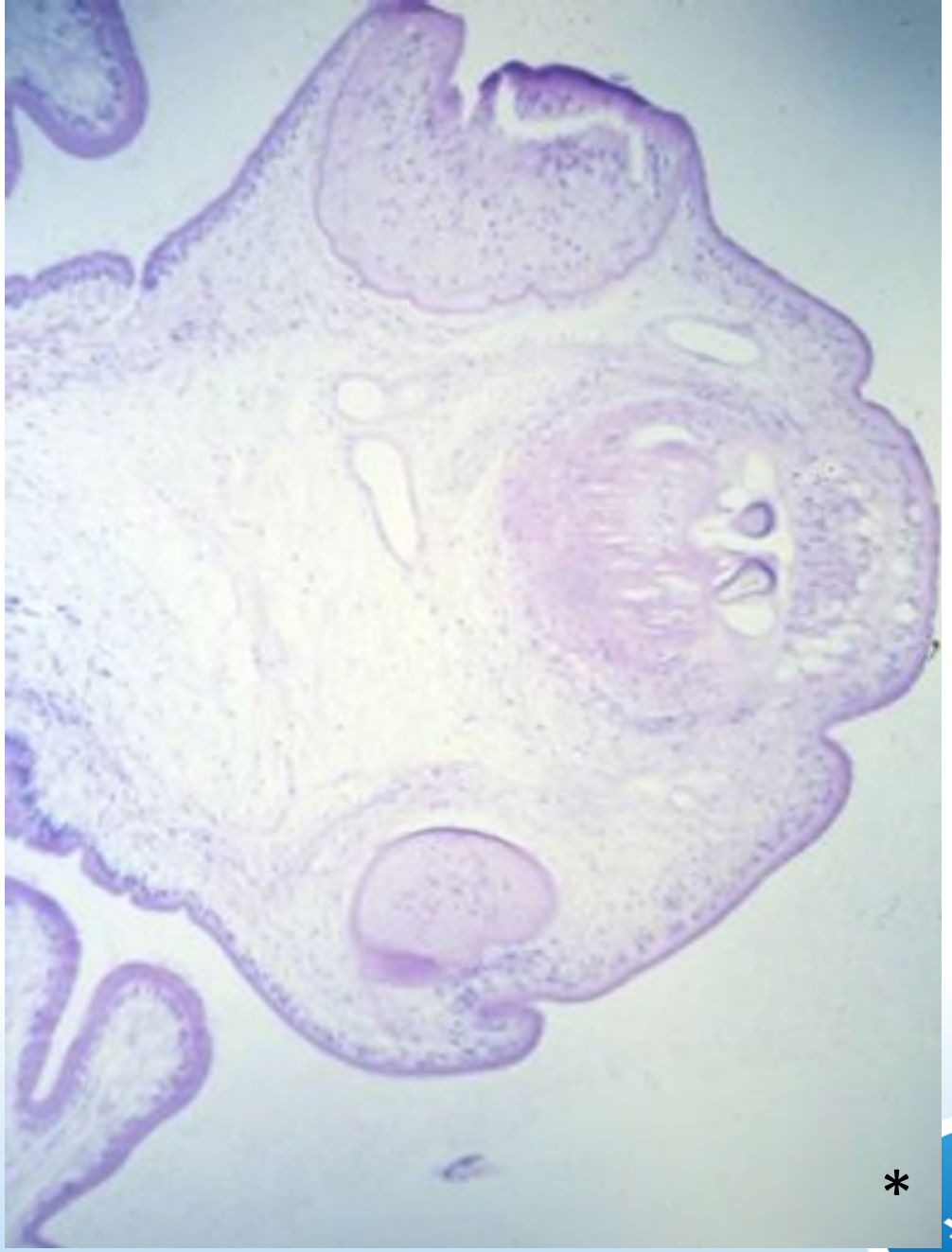


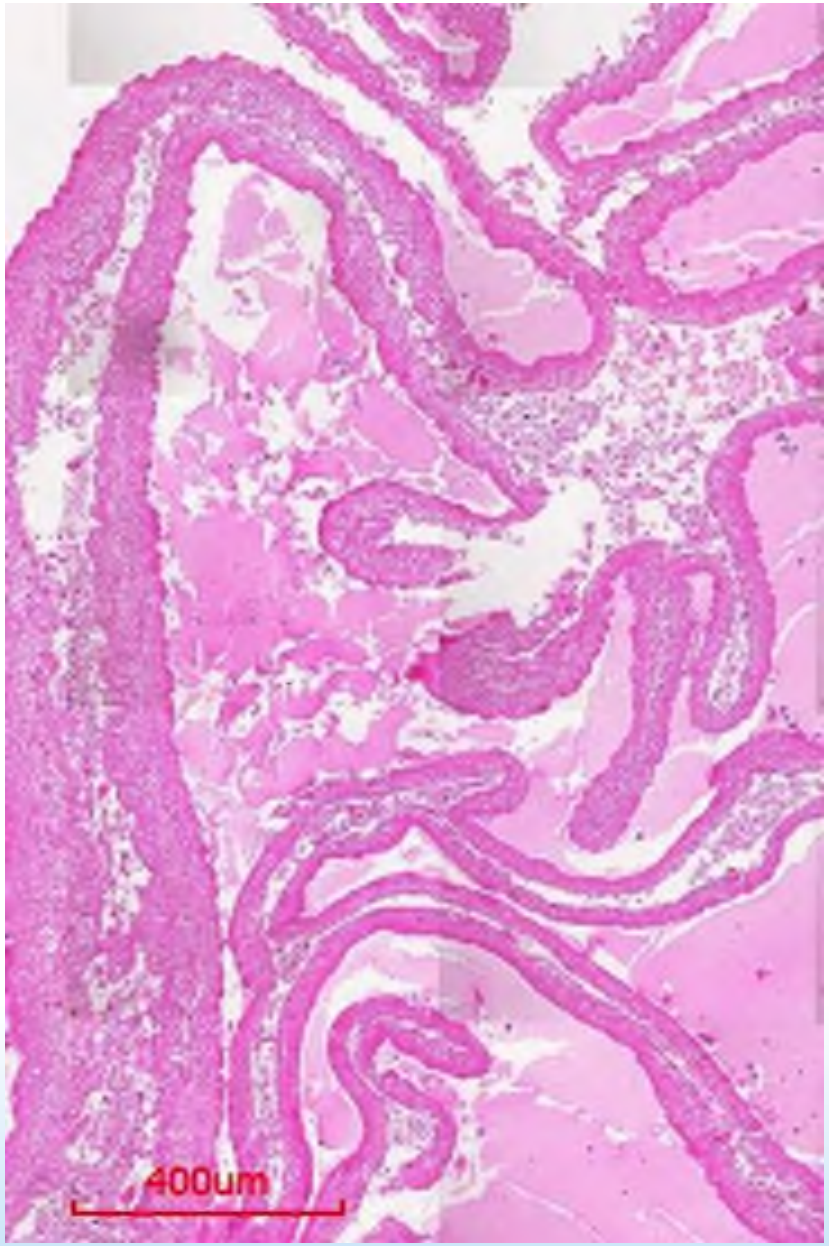
Courtesy of Dr. AC Brito

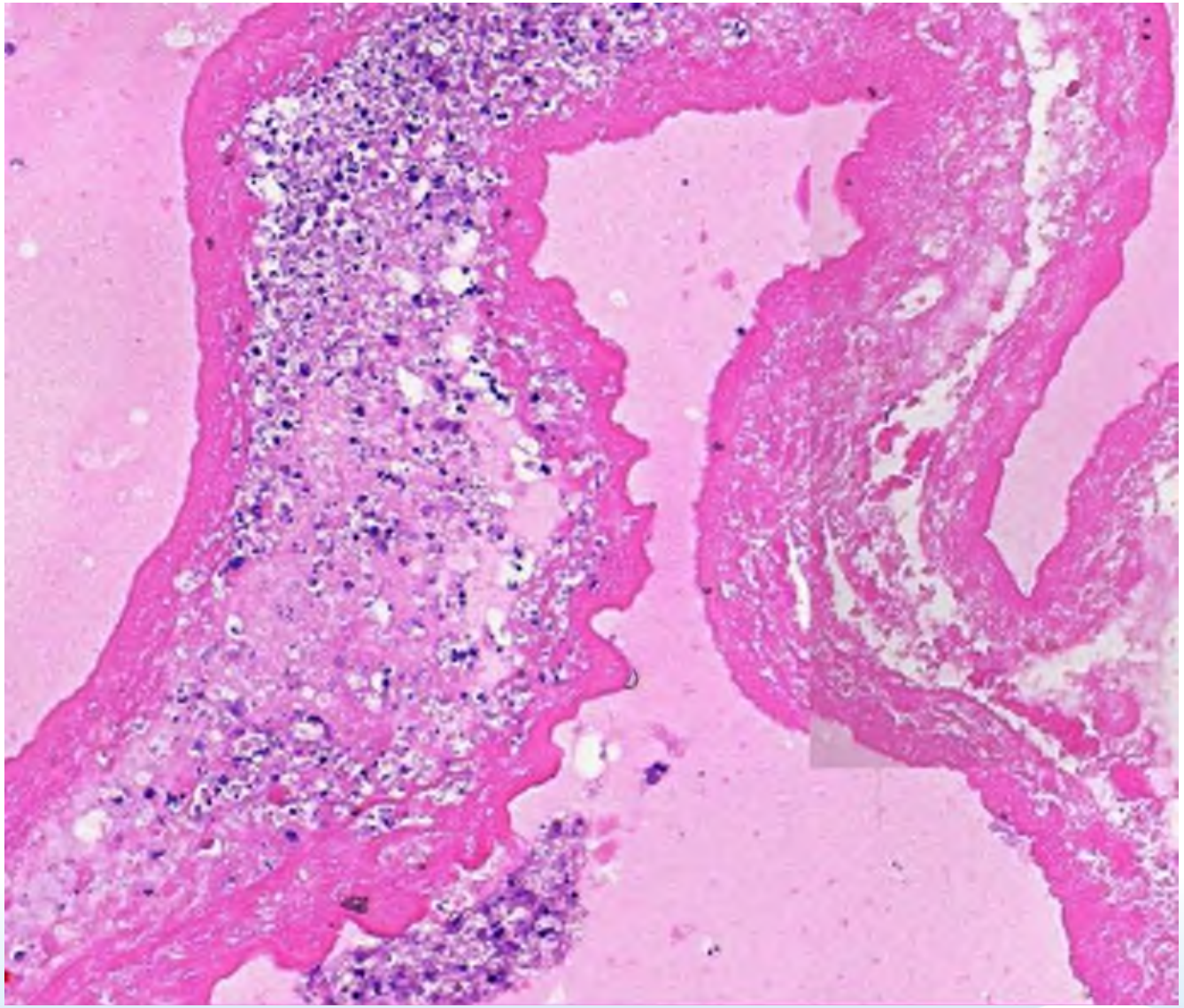


Degenerated

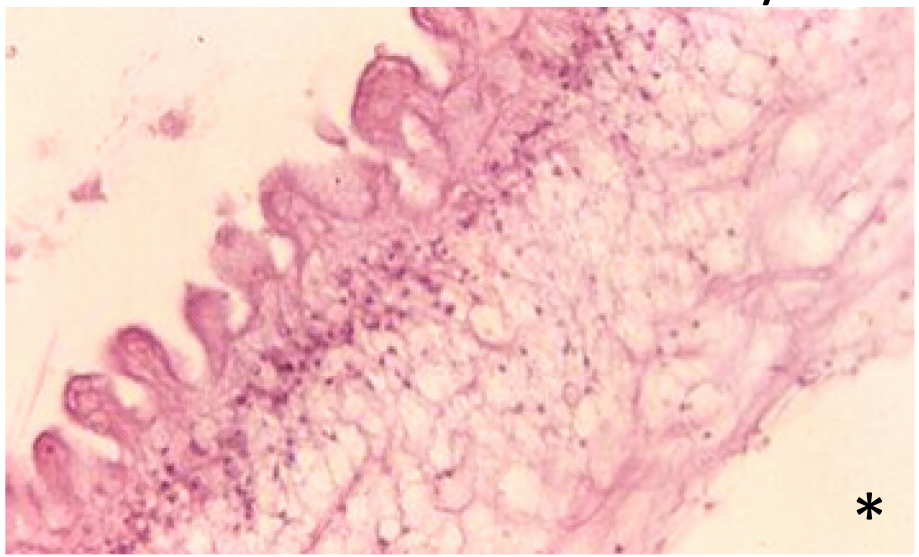


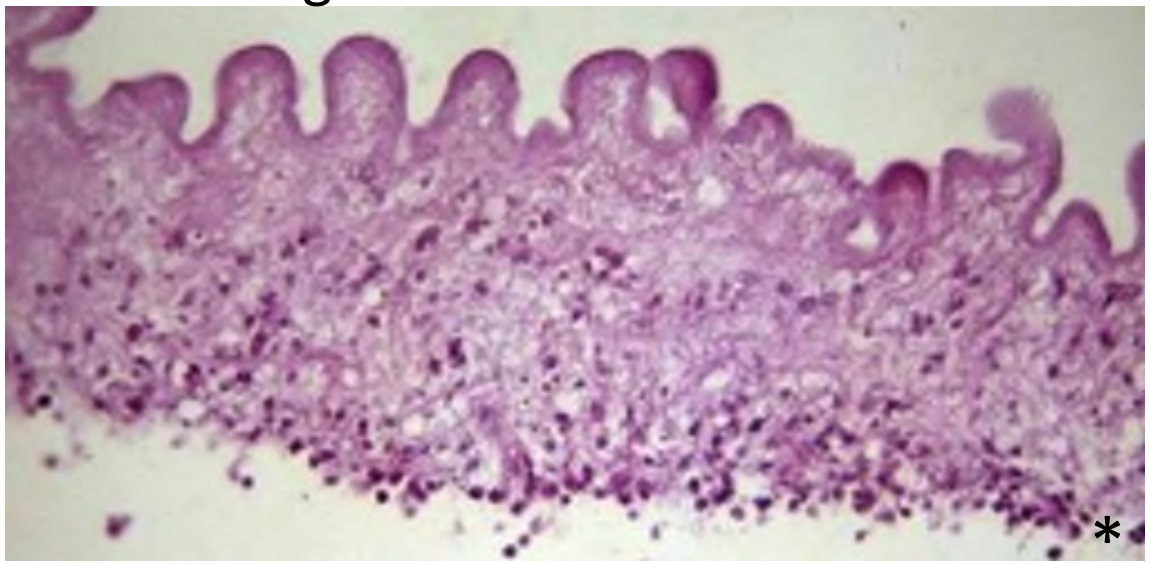


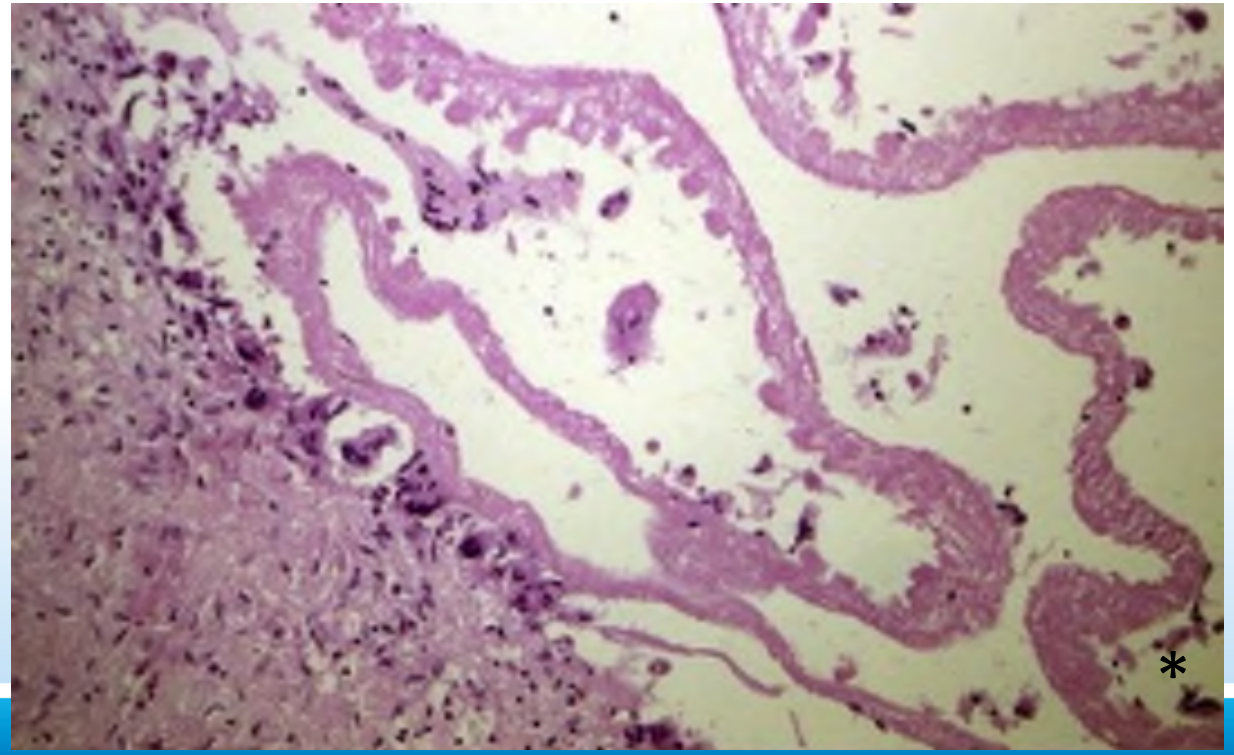

400um



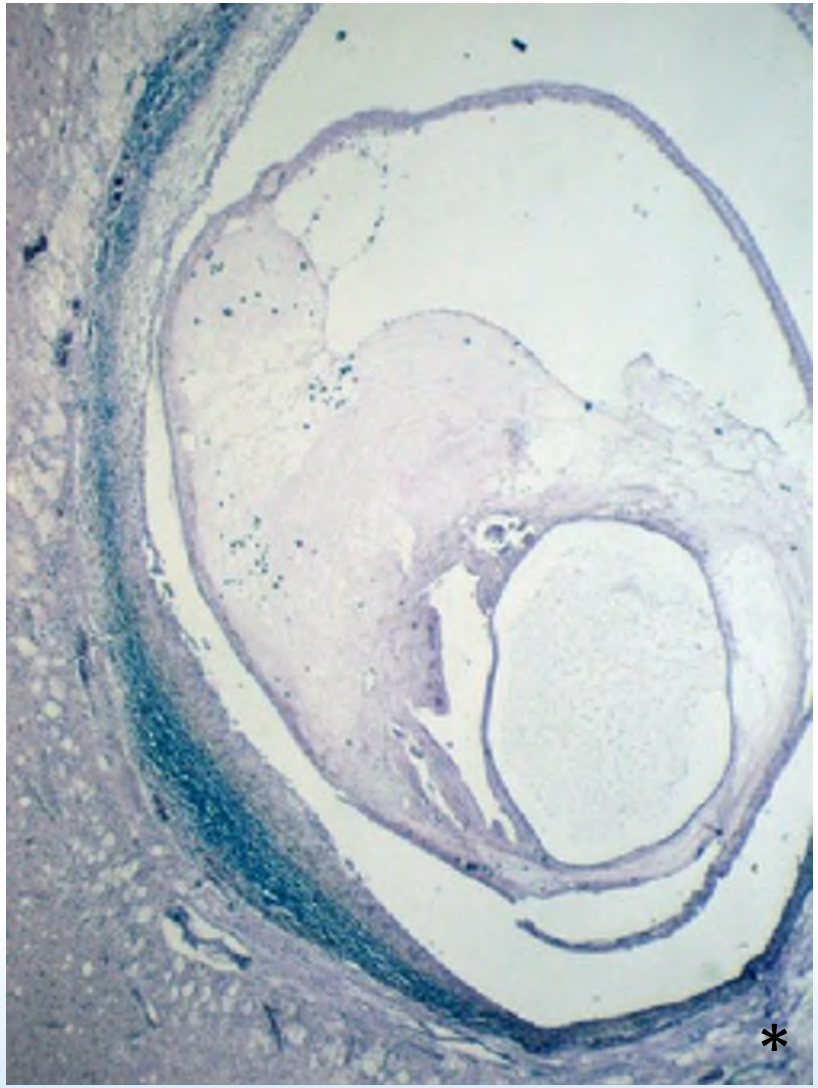
Cyst walls - various stages

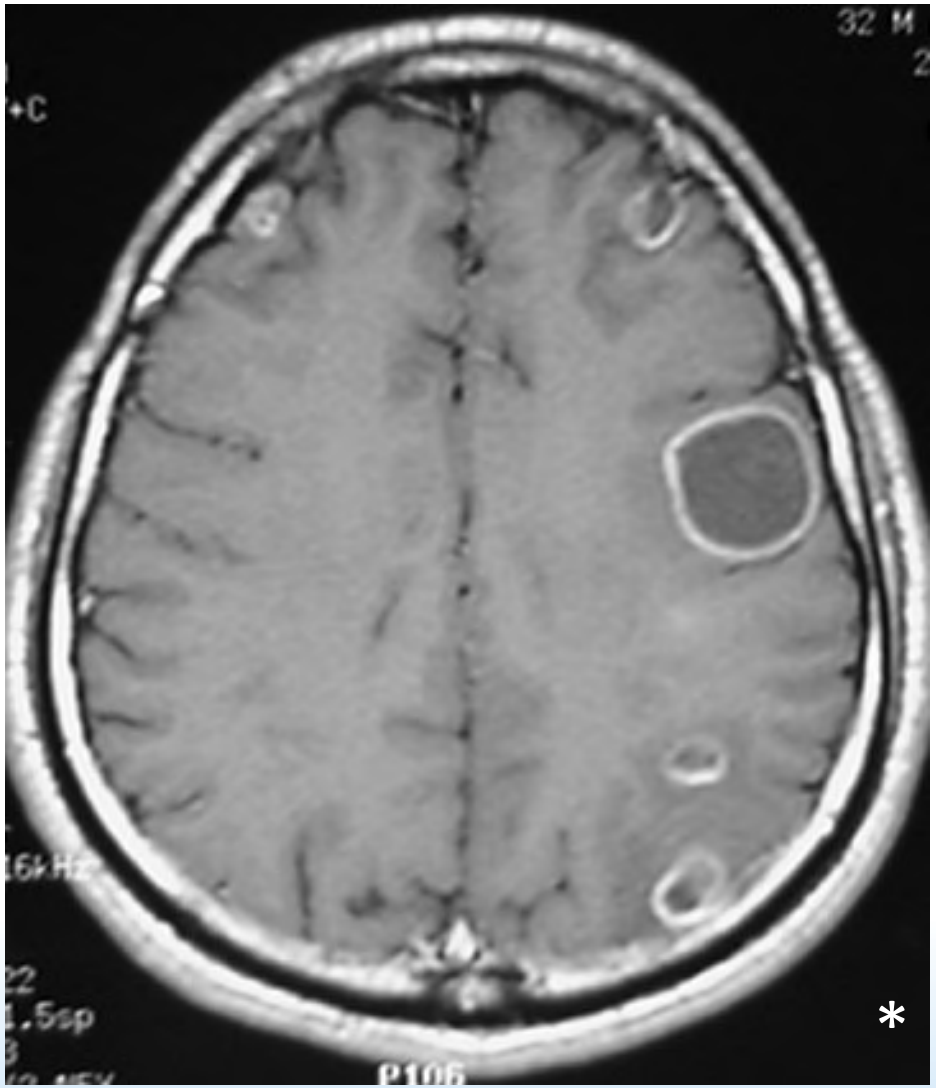




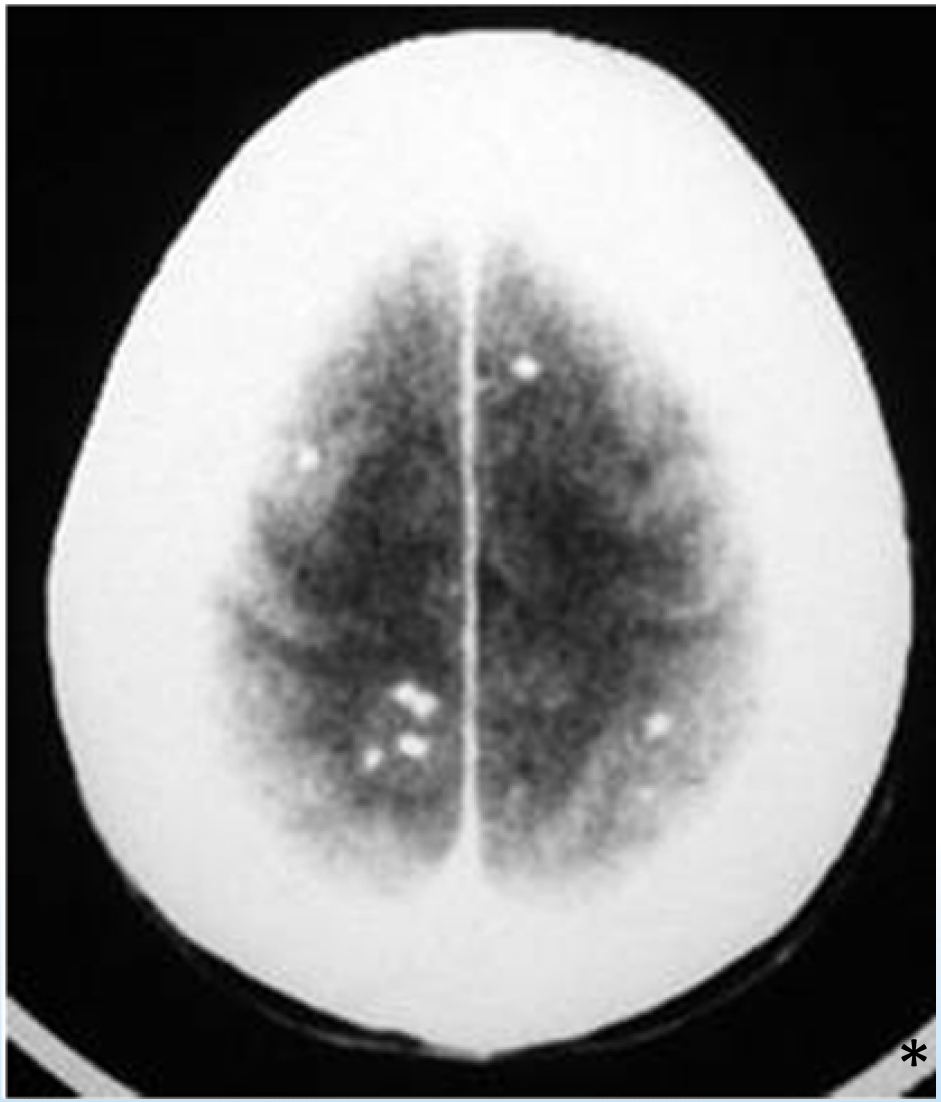


Degeneration of the cysticercus leads to inflammation

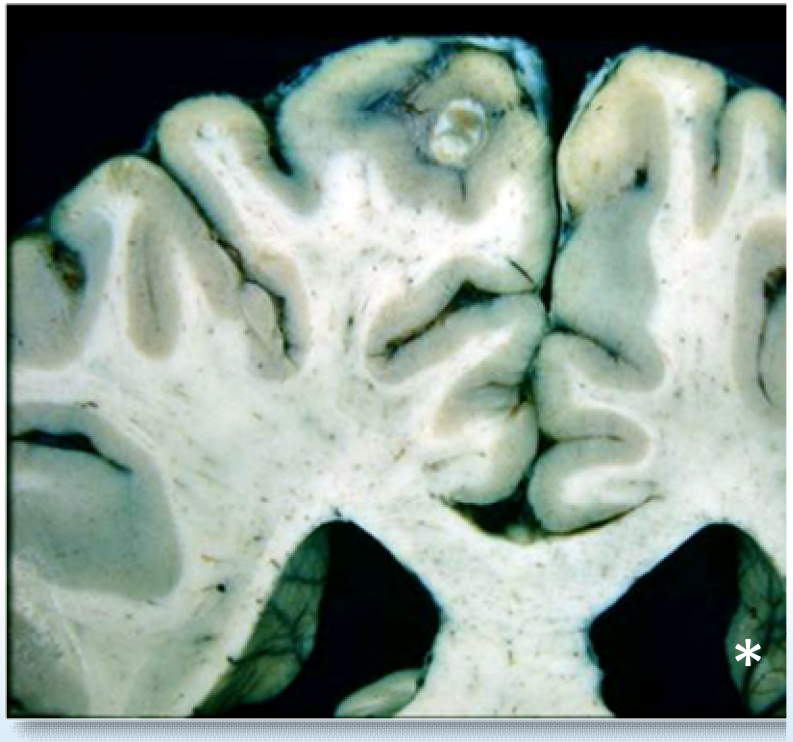


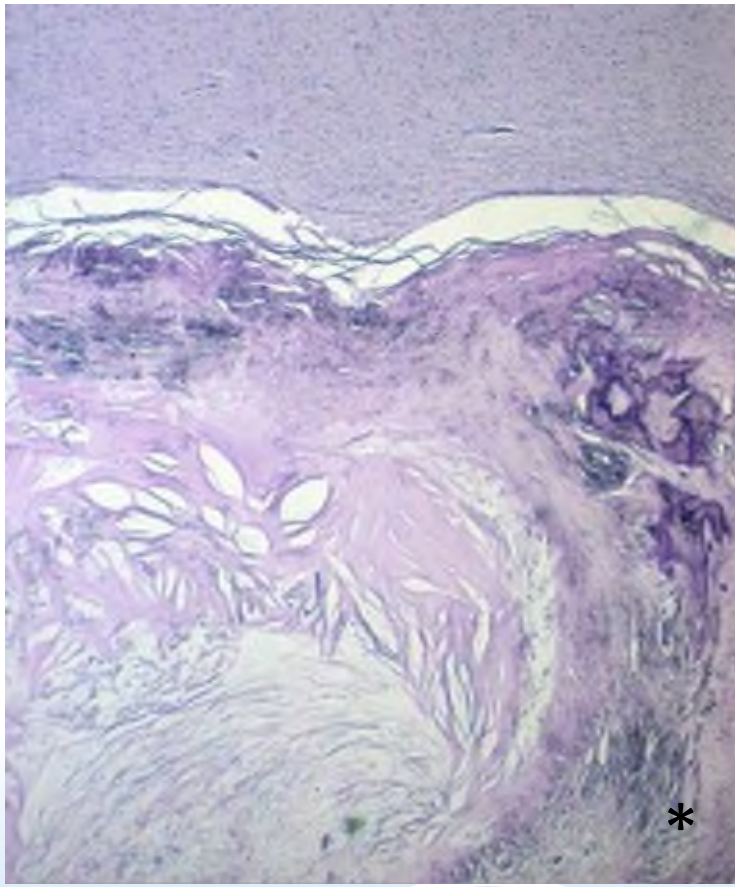


Neurocysticercosis

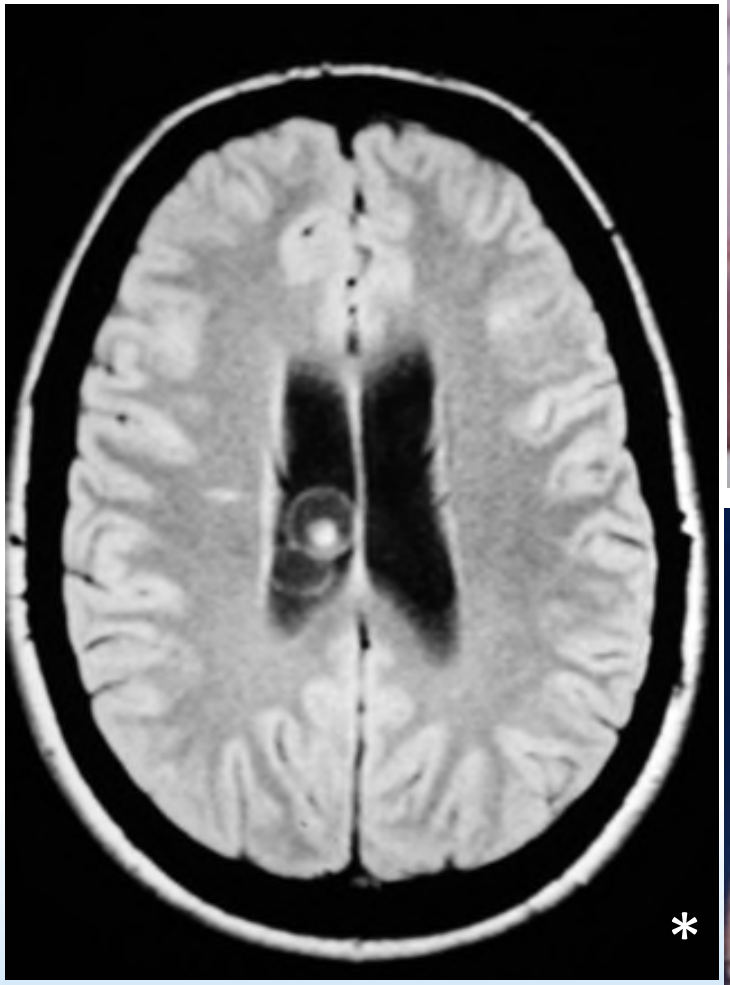


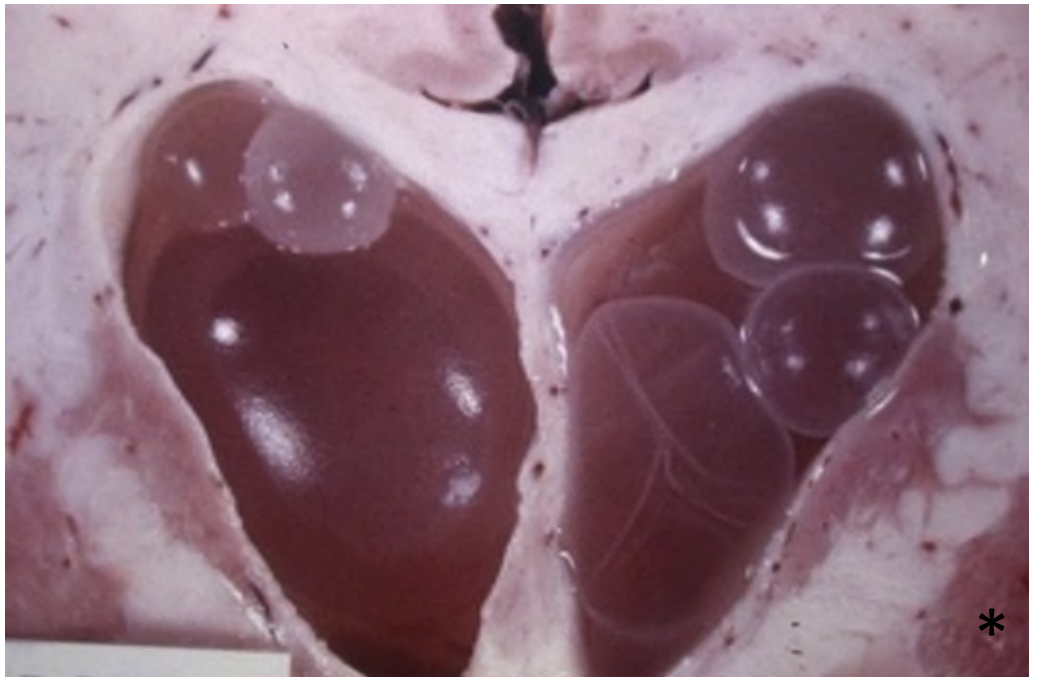
Calcification

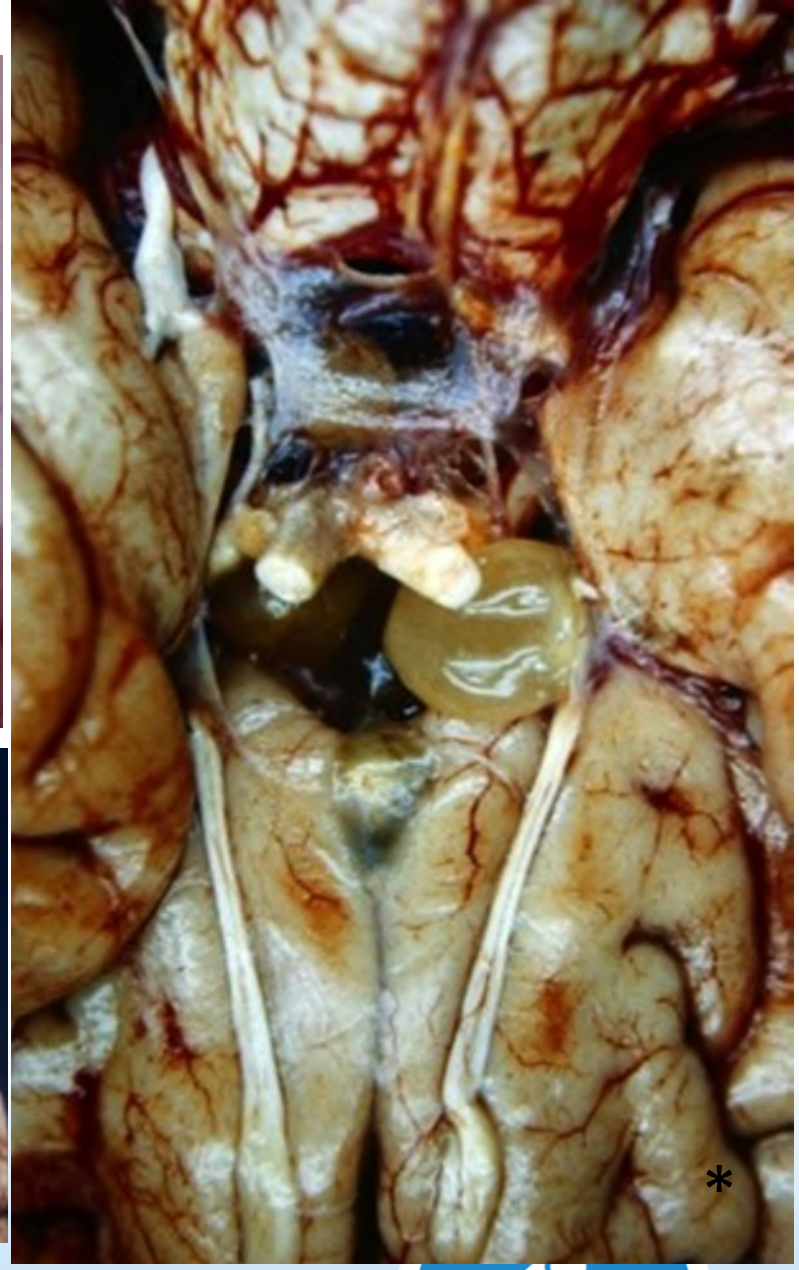




Racemose Cysticerci



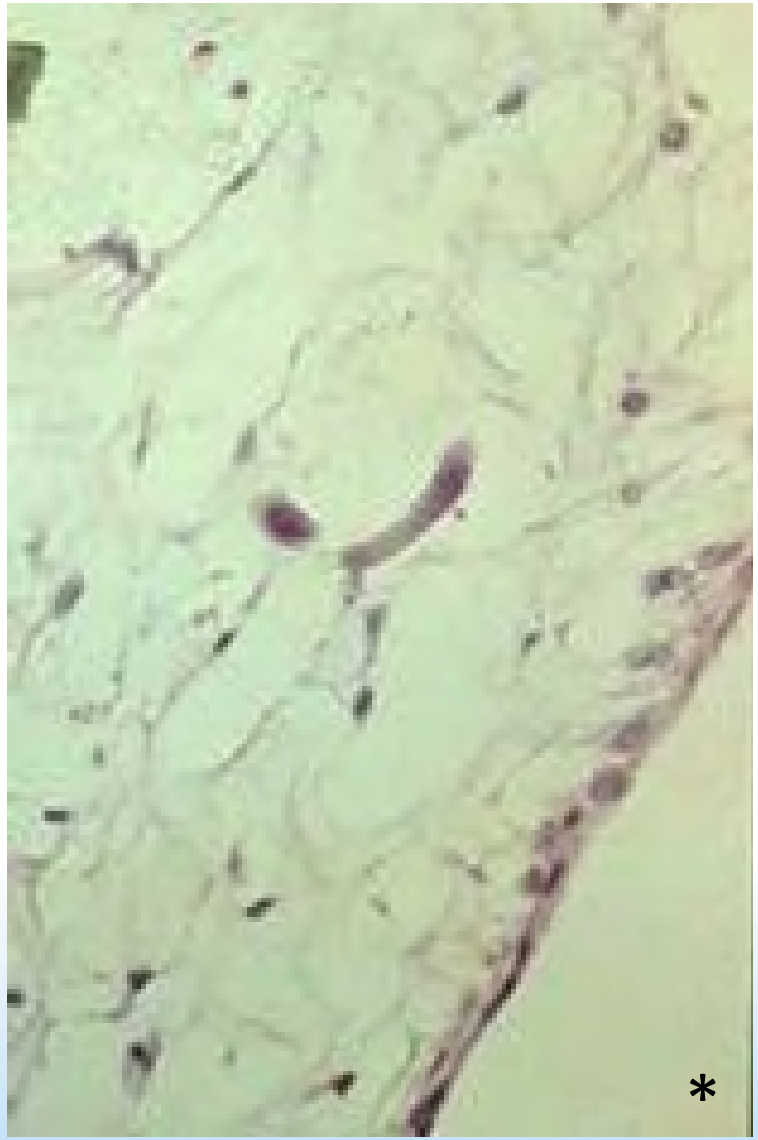




Strongyloidosis

- Strongyloides stercoralis
- Wide geografical distribution, but commonest in the tropics
- Worms live in dump warm soil, deposit eggs, transform in larvae that penetrate skin.
- Larvae pass through lungs, mature in duodenum and jejunum.
- During systemic migration may end up in ectopic sites such as the CNS
- Immunosupression cause massive intestinal growth of worms, colonic ulceration and septicemia.

Strongyloides in the CSF (left) and subaracnoid space (right) of patient who died with AIDS

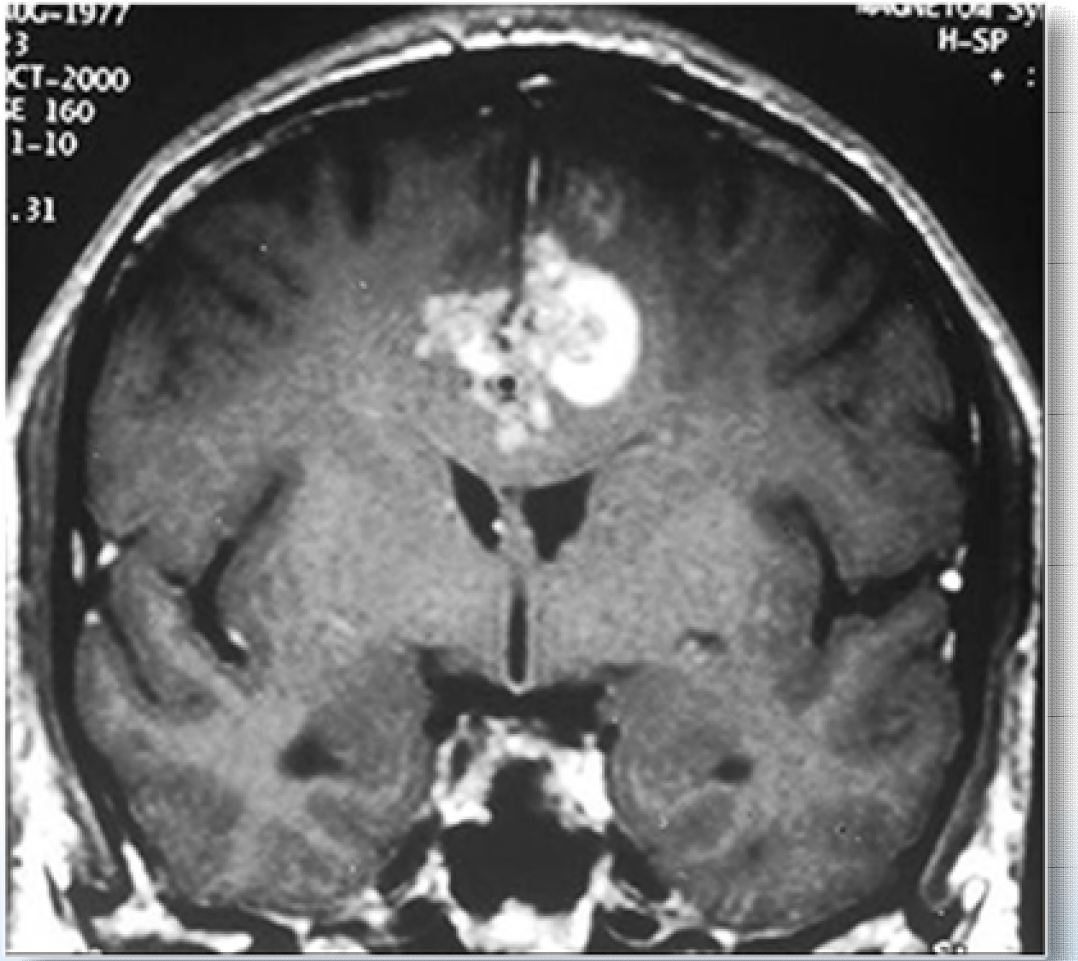


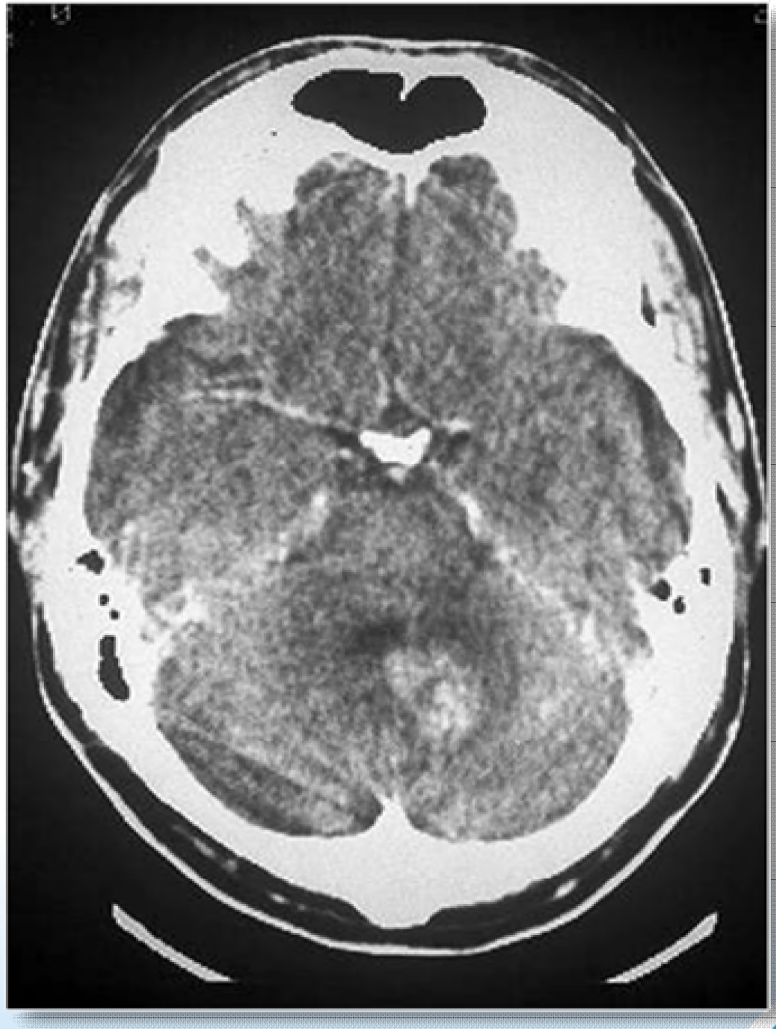
Schistosomiasis

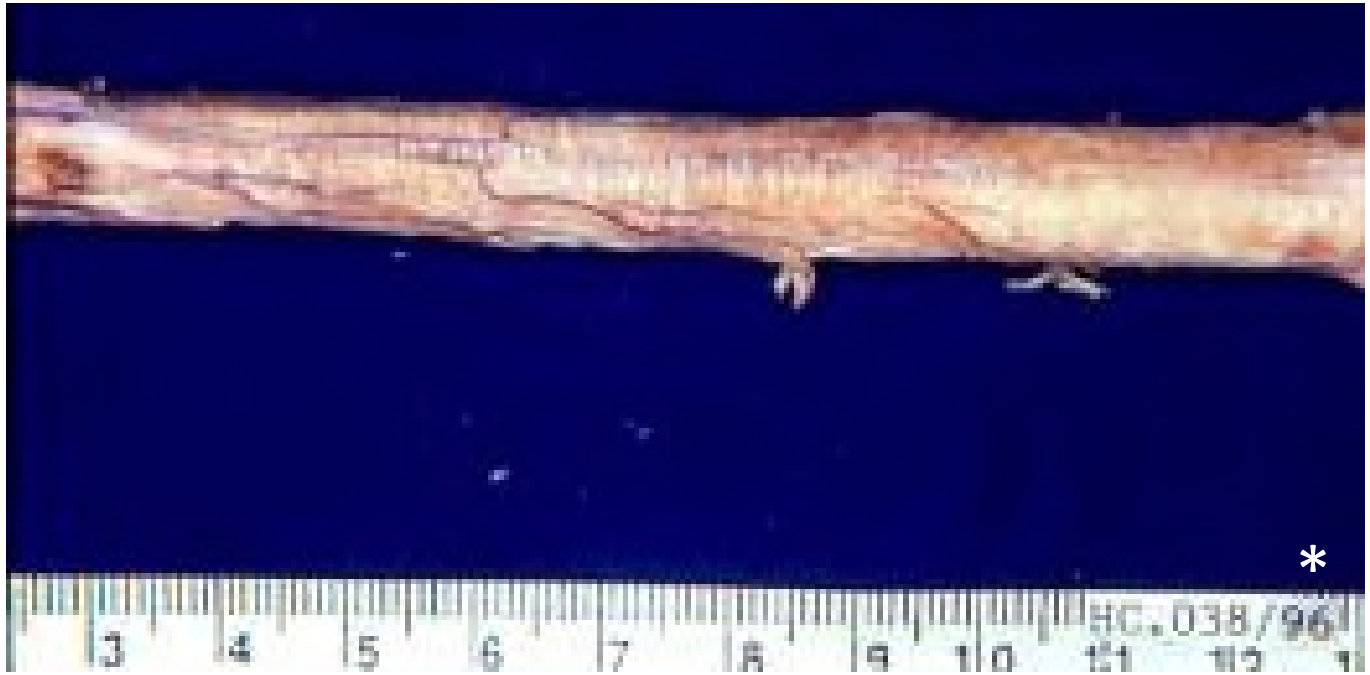
- Schistosoma *mansoni, japonicum, hematobium* (Latin America, Asia and Africa)

Neuro-schistosomiasis

- CNS involvement is uncommon
- Ova reach the CNS by retrograde passage through the portal mesenteric and pelvic veins and valveless vertebral venous plexus of Batson.
- Anomalous migration of the adult close to CNS and in-situ egg deposition
- Thoracic and lower spinal cord are common locations


H-SP

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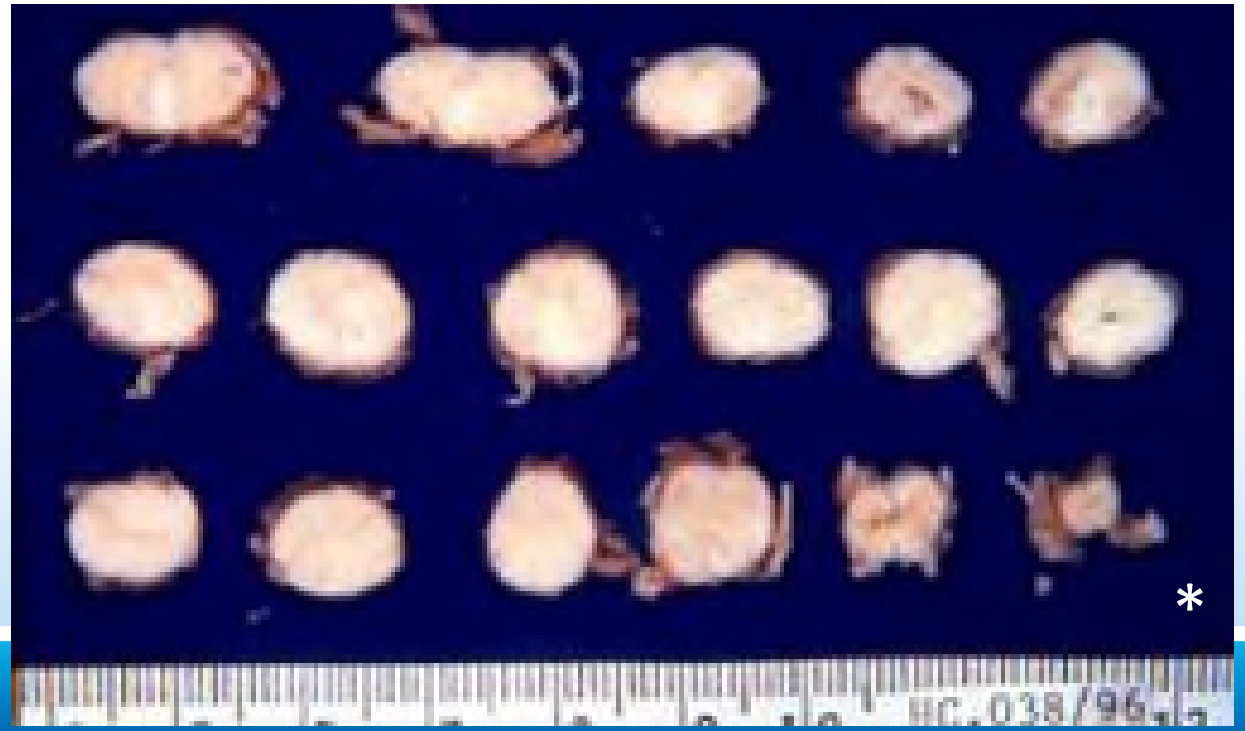
HC.038/96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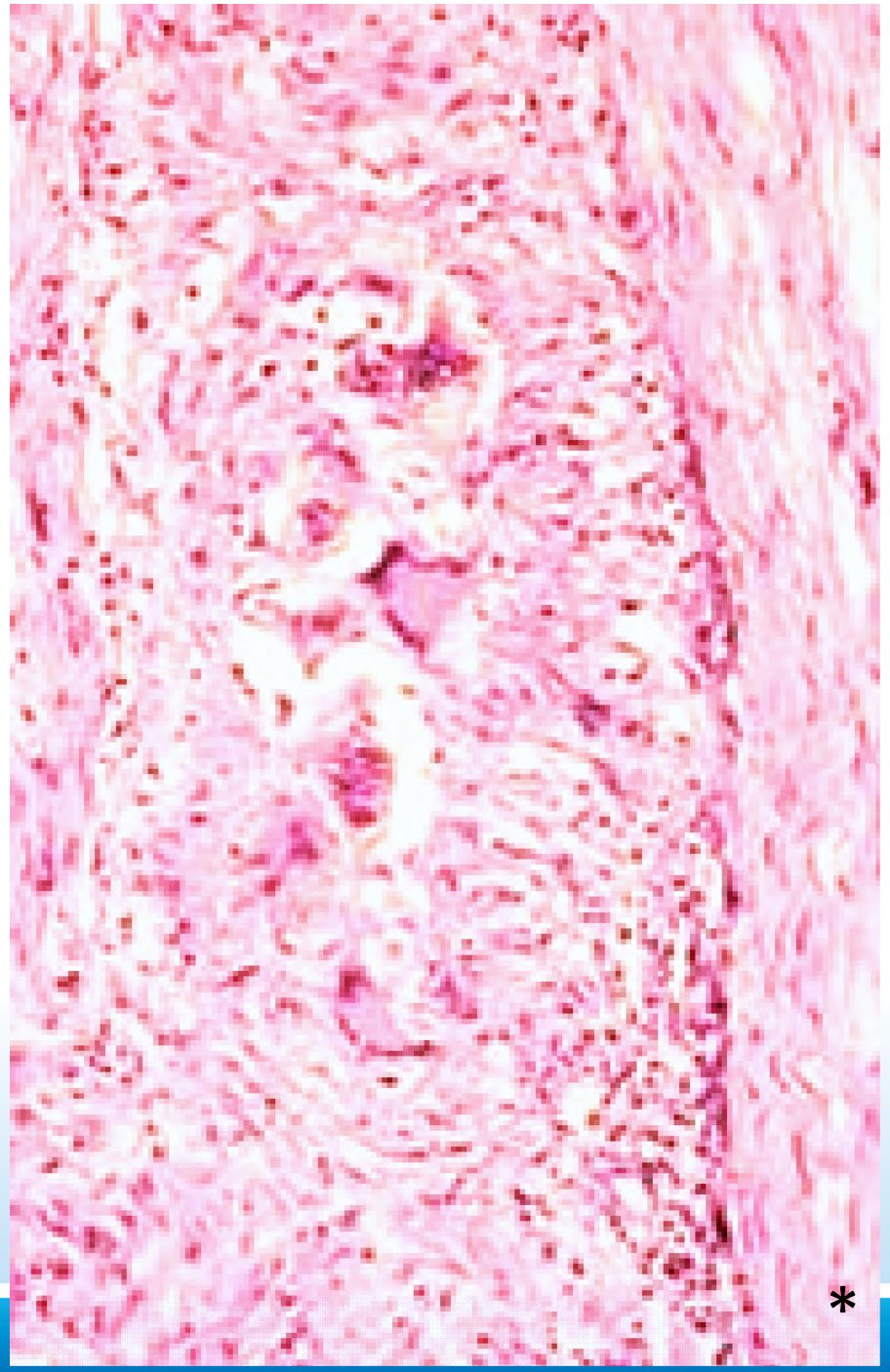
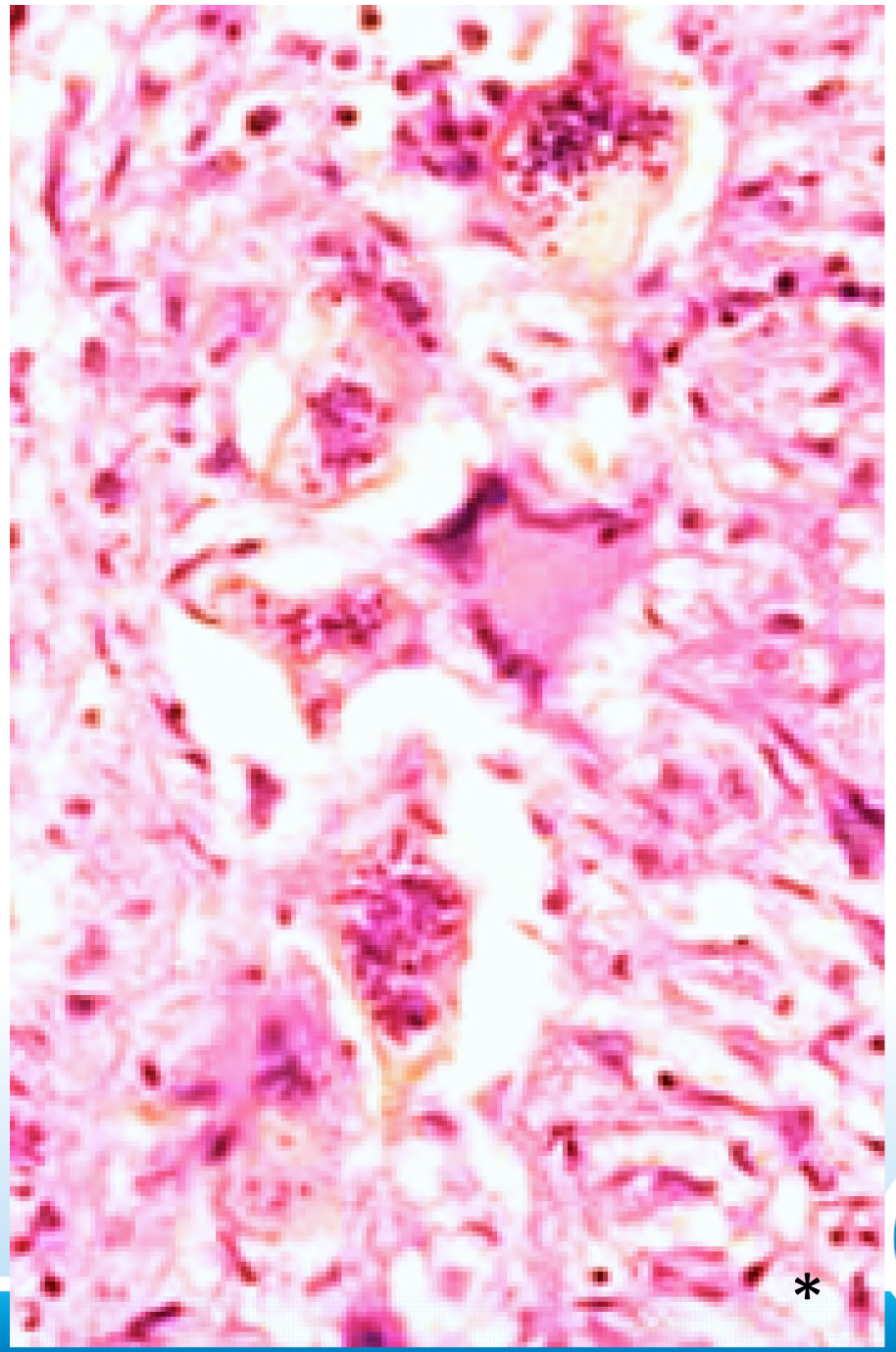
HC.038/96





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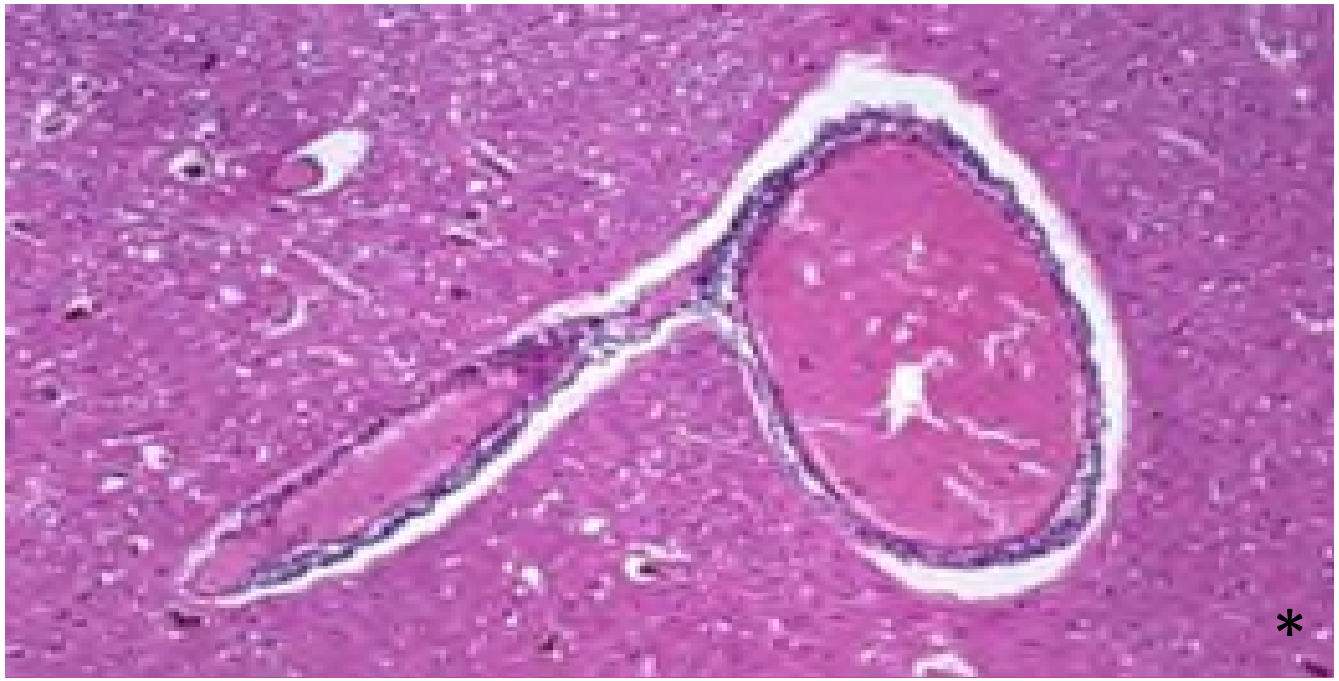
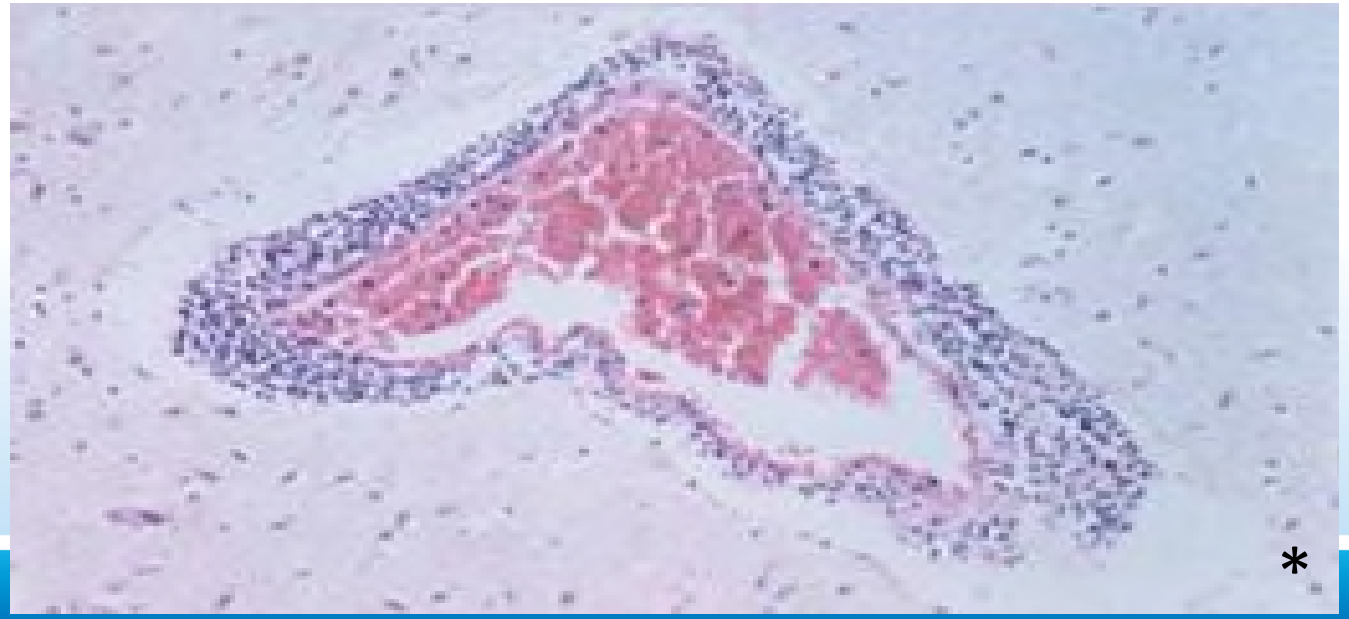
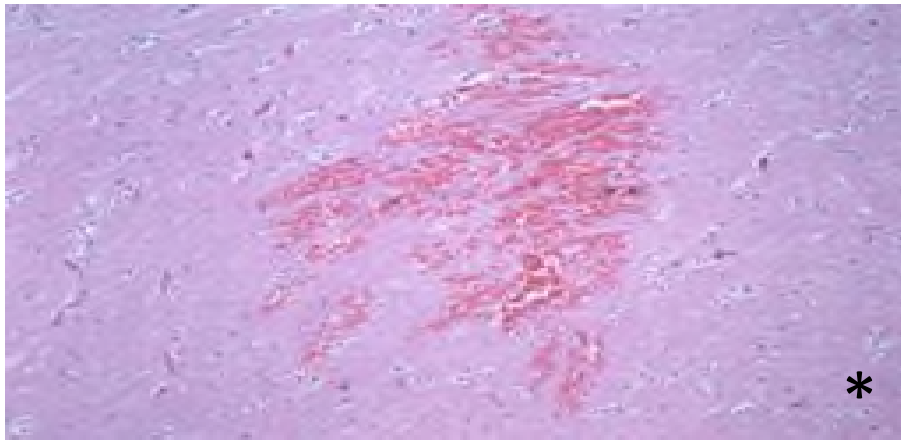
Arboviruses

- Important cause of morbidity and mortality in many tropical regions
- Limited geographical distribution due to the necessity of climatic conditions for the insects to live.
- Dengue virus (Flavivirus): Transmitted by mosquitos Aedes aegypti
- Causes benign infection but may be haemorrhagic

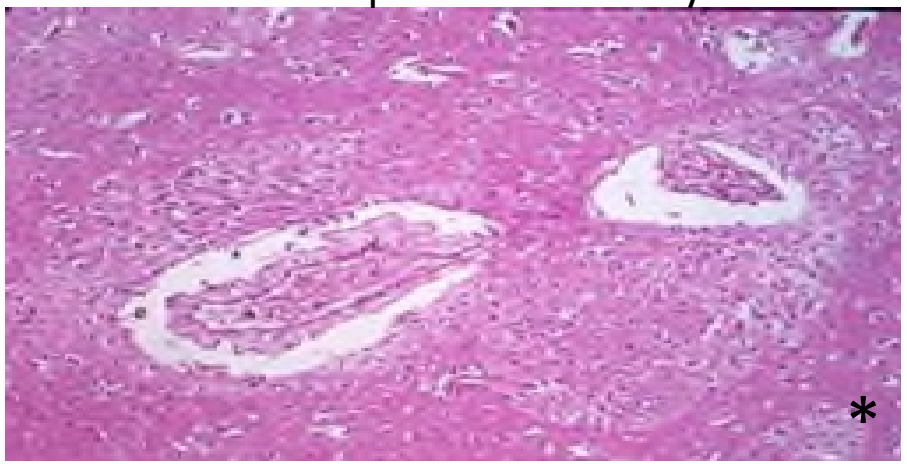
Dengue

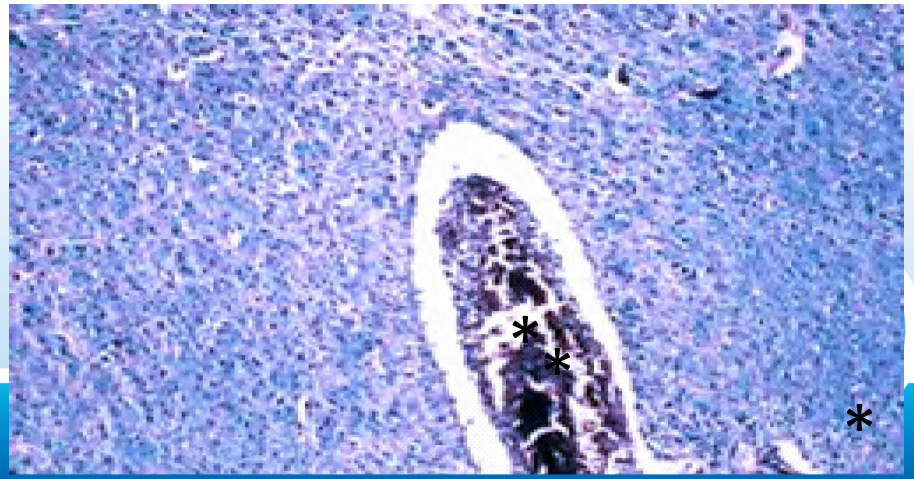






Post-infectious perivenous demyelination

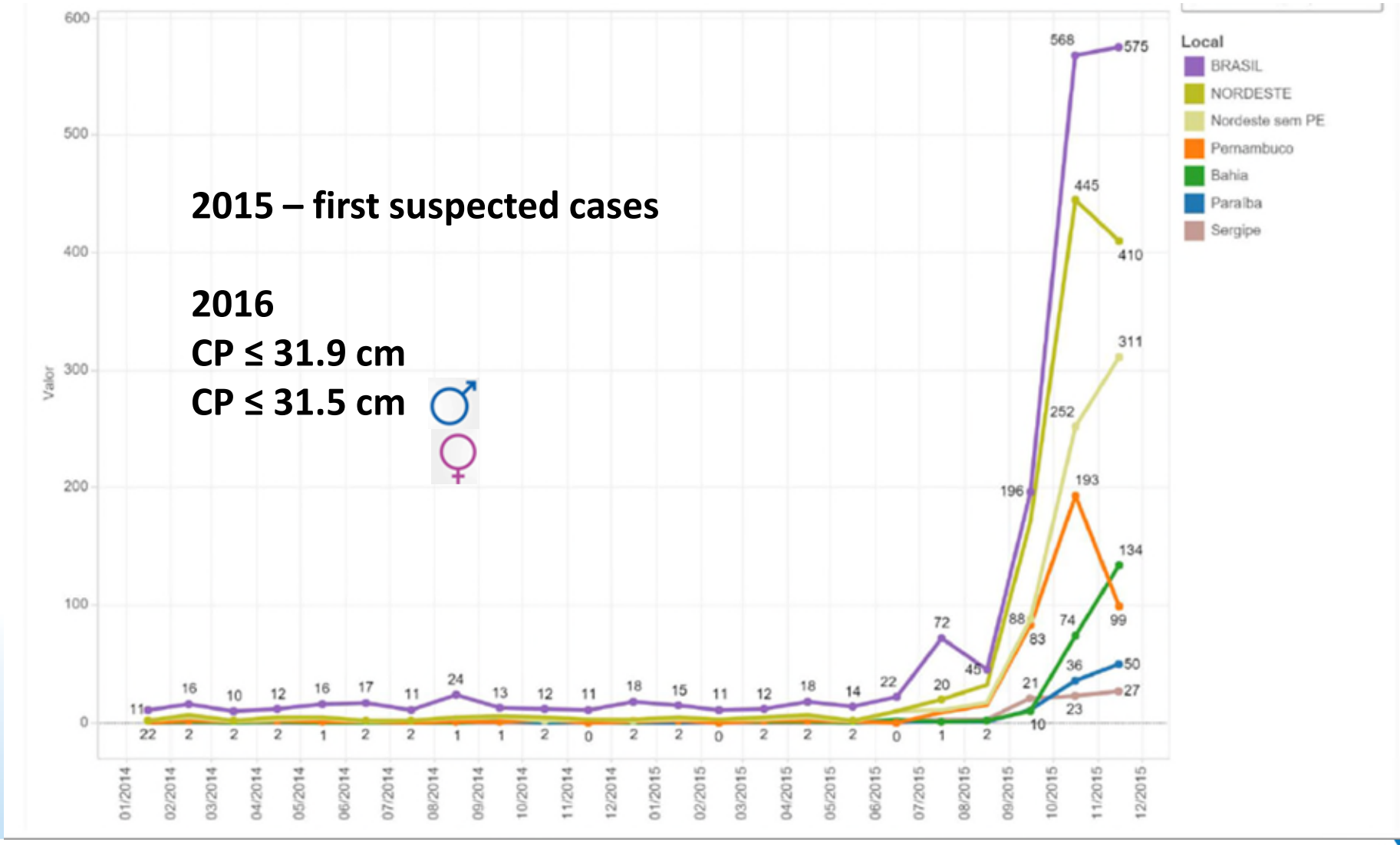




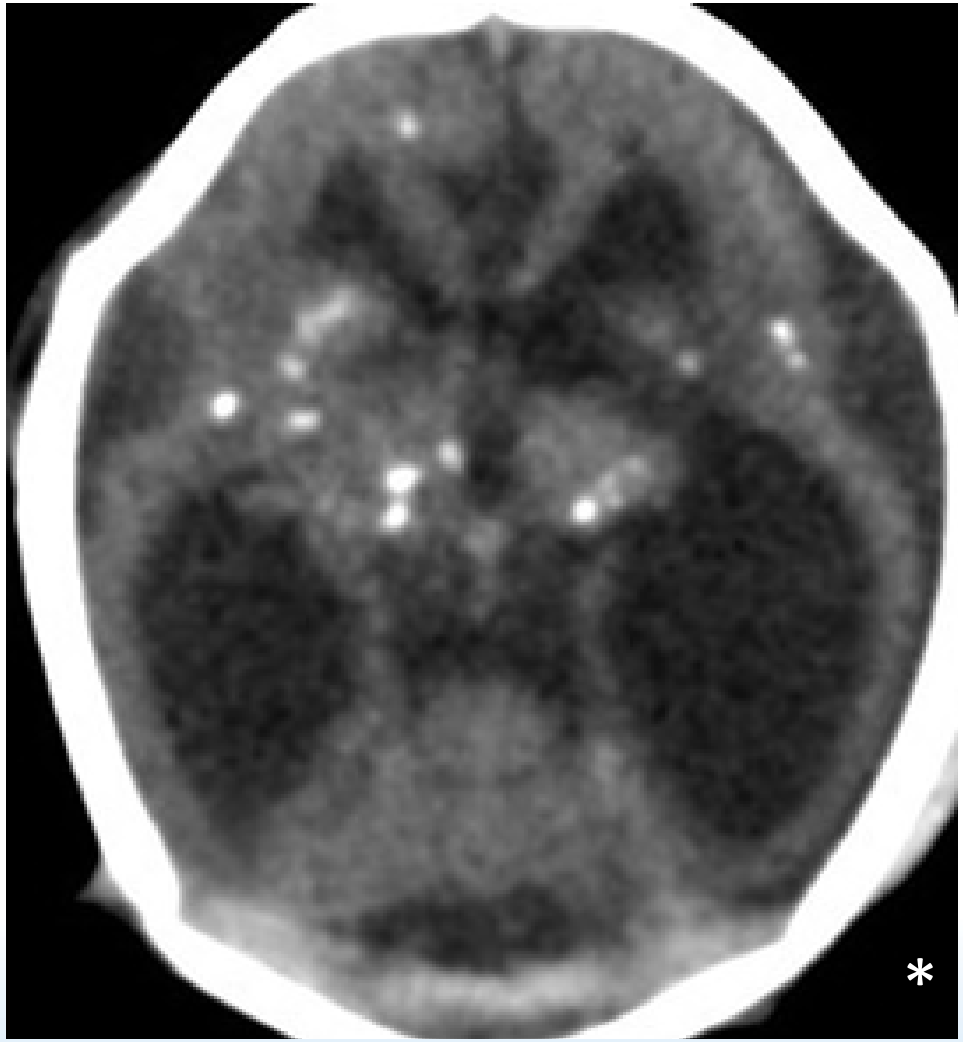
- Zika virus (ZIKV) - a flavivirus transmitted by the mosquito Aedes *aegypti*.

- Human infection varies from mild fever, arthralgia, rash, headache, and myalgia, but may be asymptomatic.

Microcephaly in Brazil – 2000 - 2015



http://portalsaude.saude.gov.br/images/pdf/2016/fevereiro/12/COES-Microcefalias-Informe-Epidemiologico-12-SE-05-2016-12fev2016-13h30.pdf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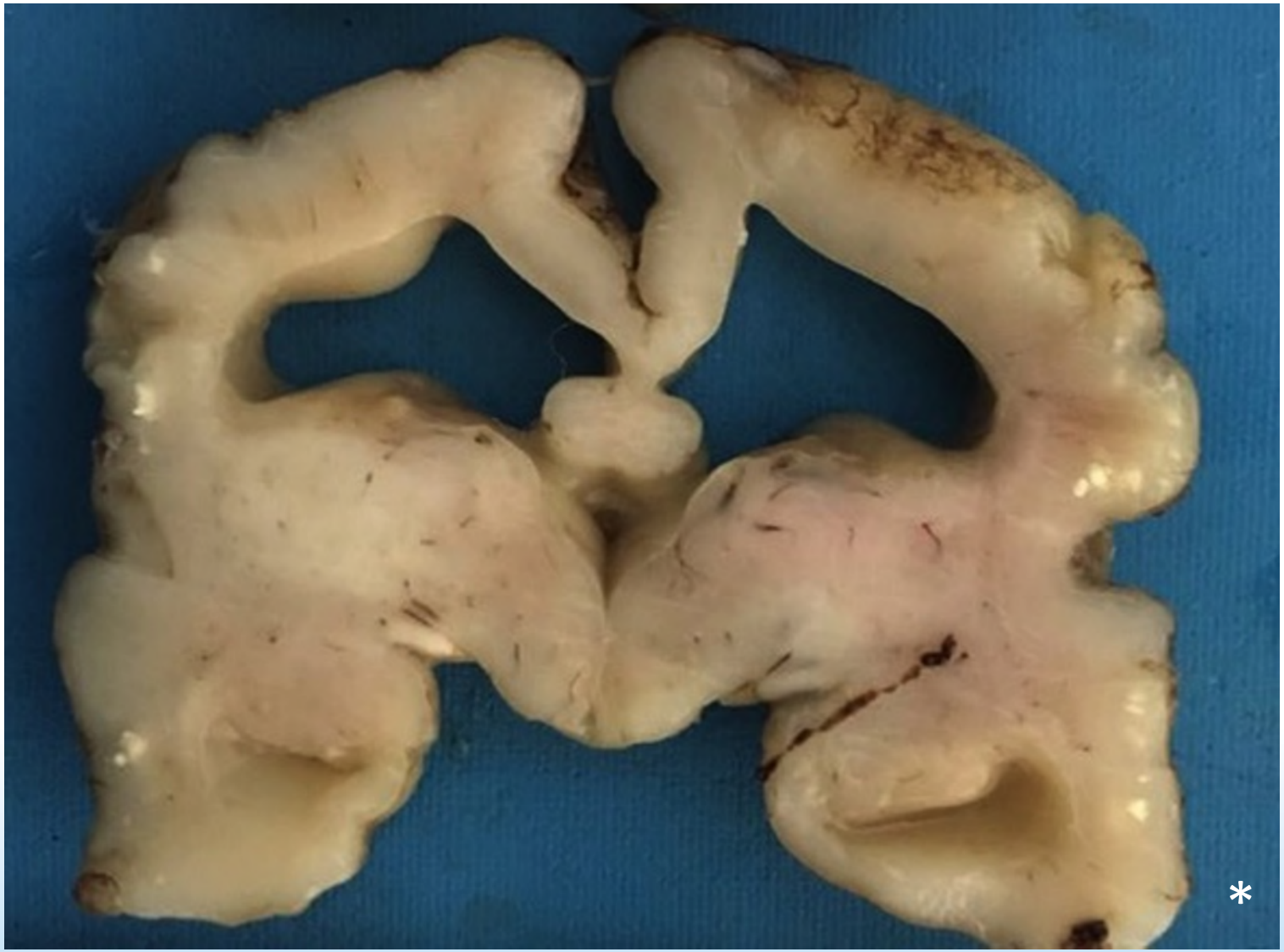
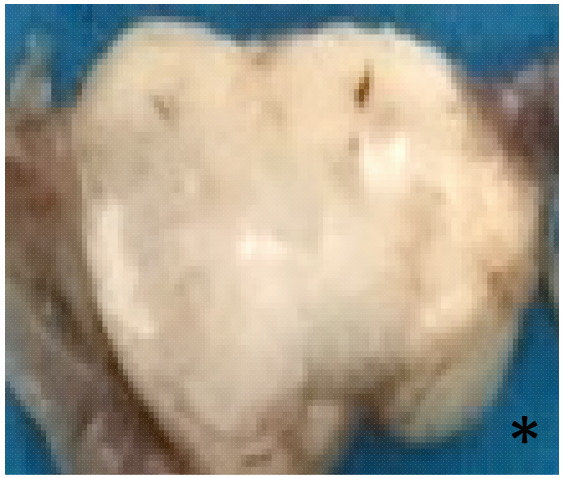
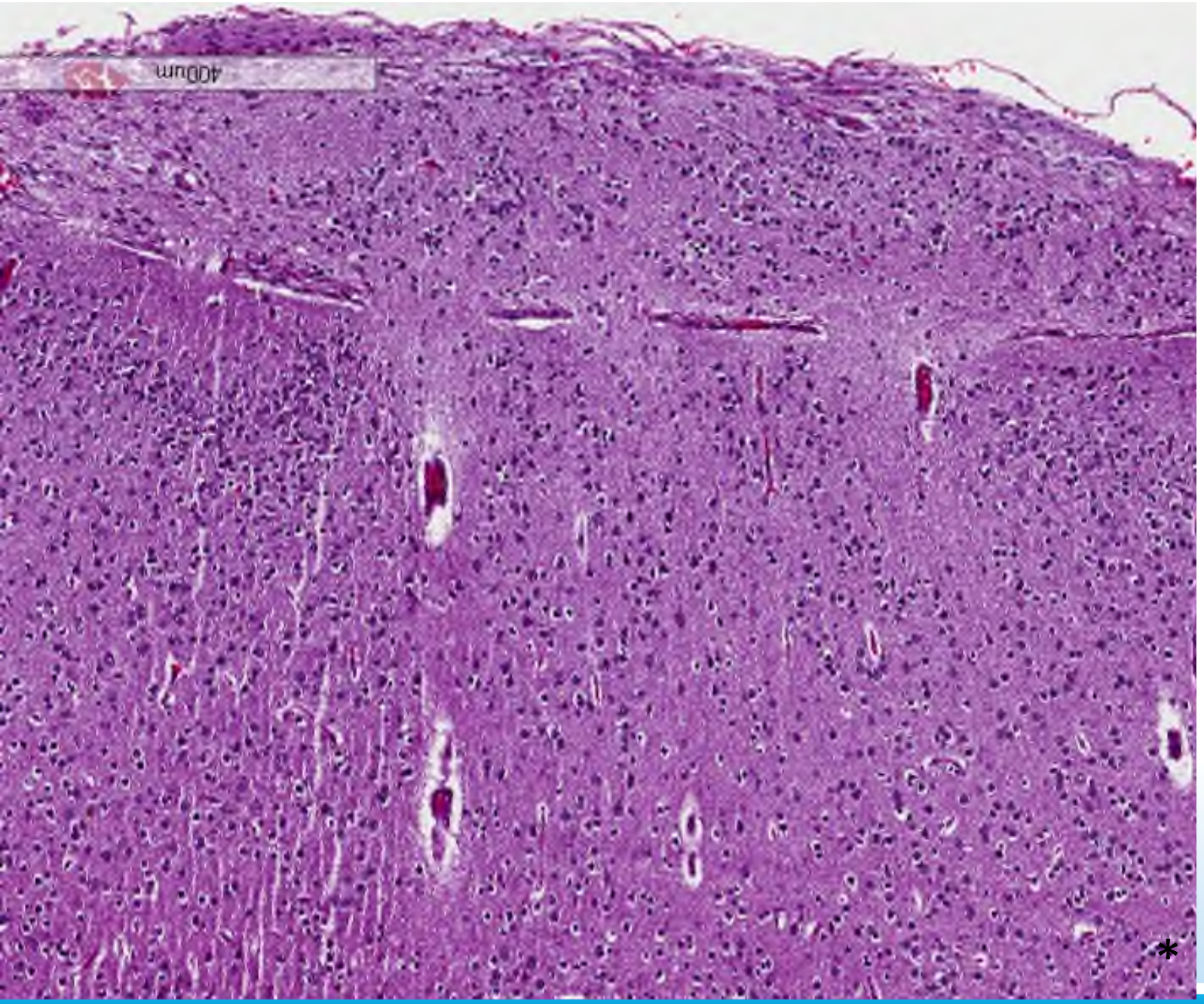
Ex vacuo ventriculomegaly and calcifications



Obstructive hydrocephalus



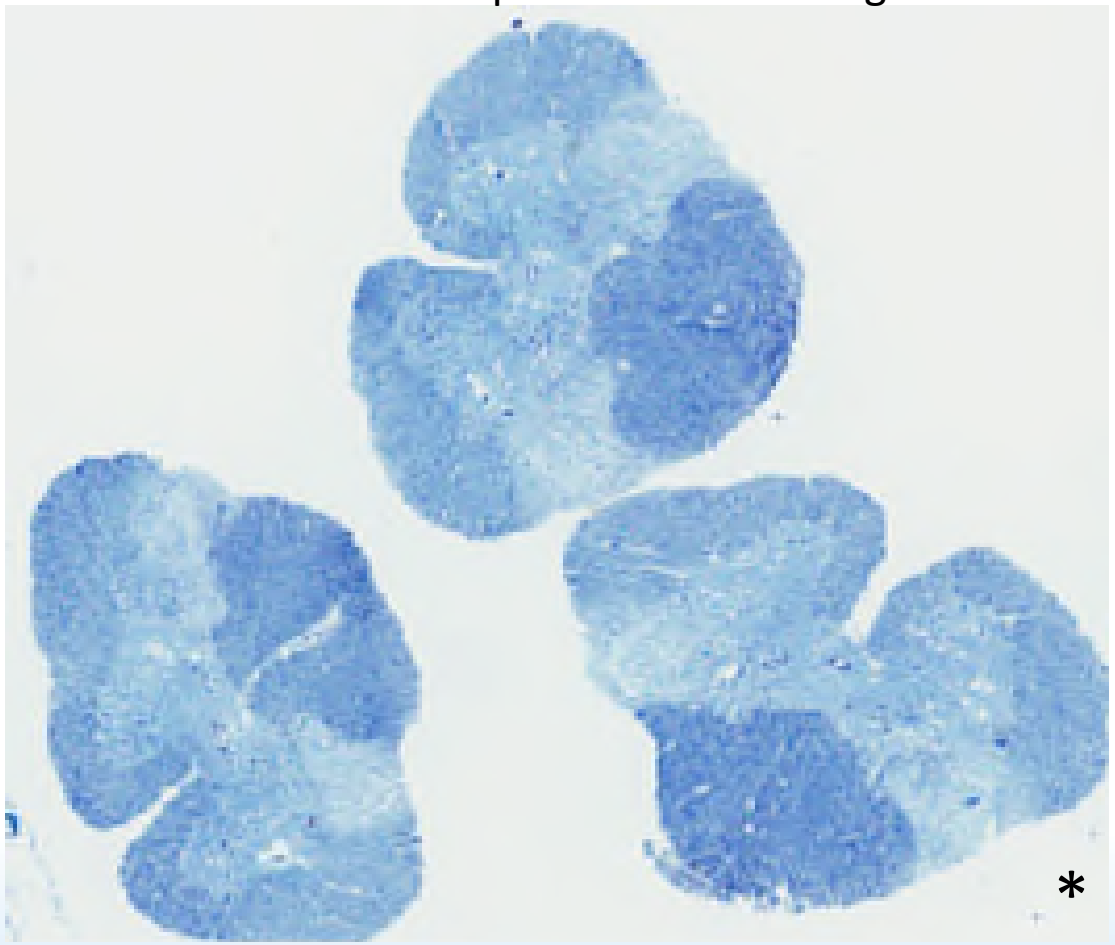


Migration disturbances
Meningeal glioneuronal heterotopia

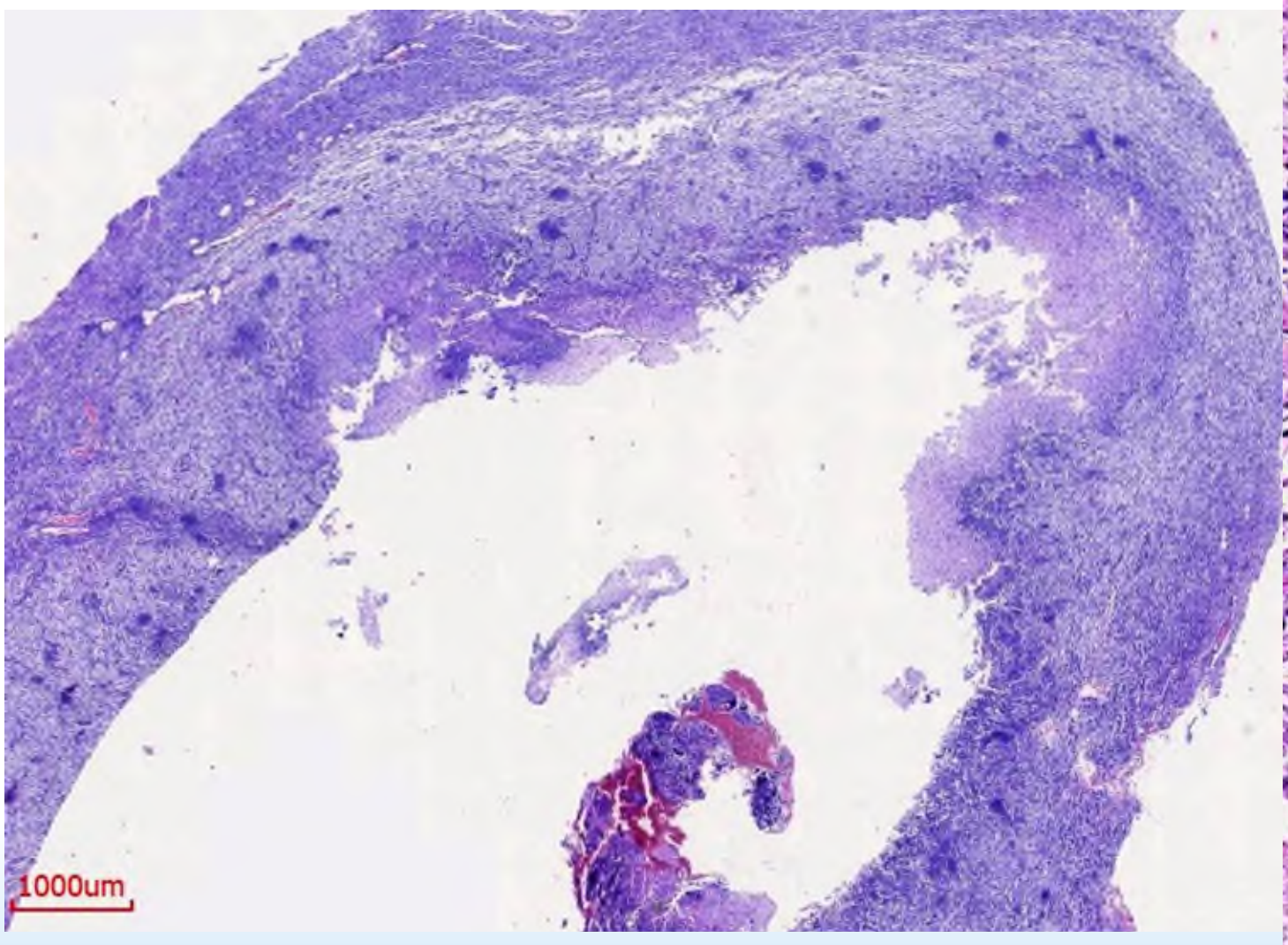
Cobblestone appearance of this smooth brain of an infant with congenital Zika syndrome

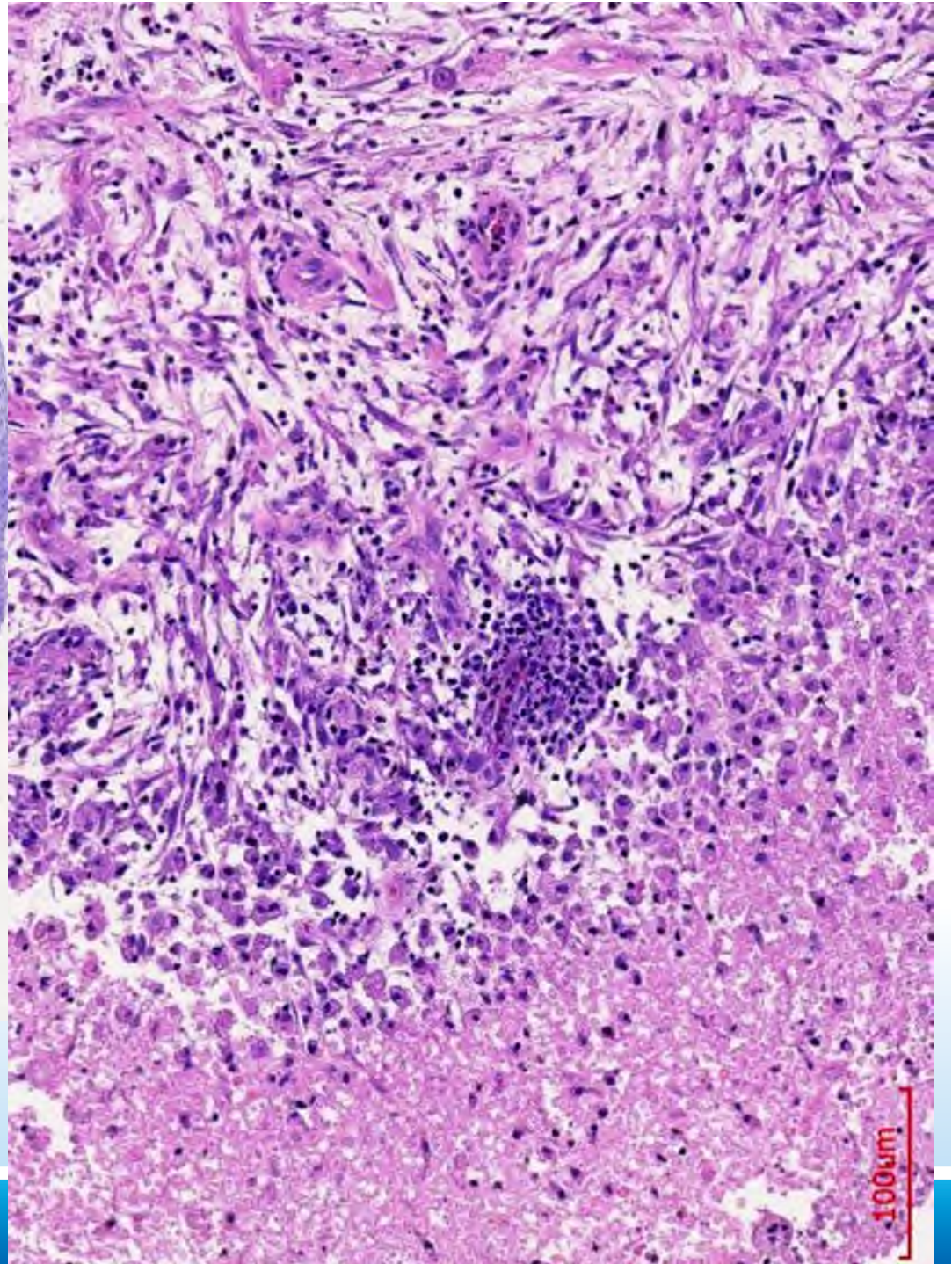
Spinal Cord

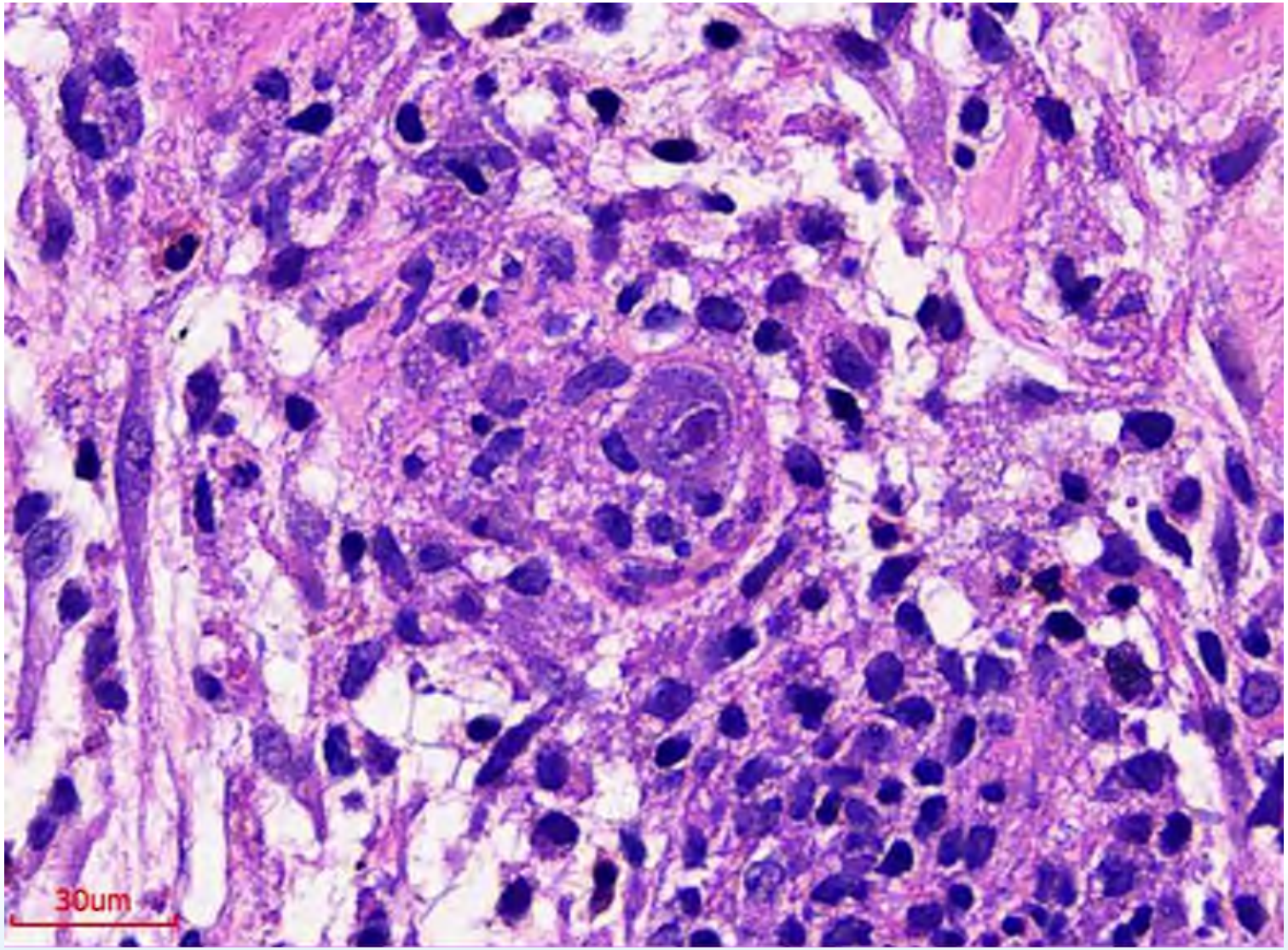
Lack of descending motor axons
The corticospinal tract is missing

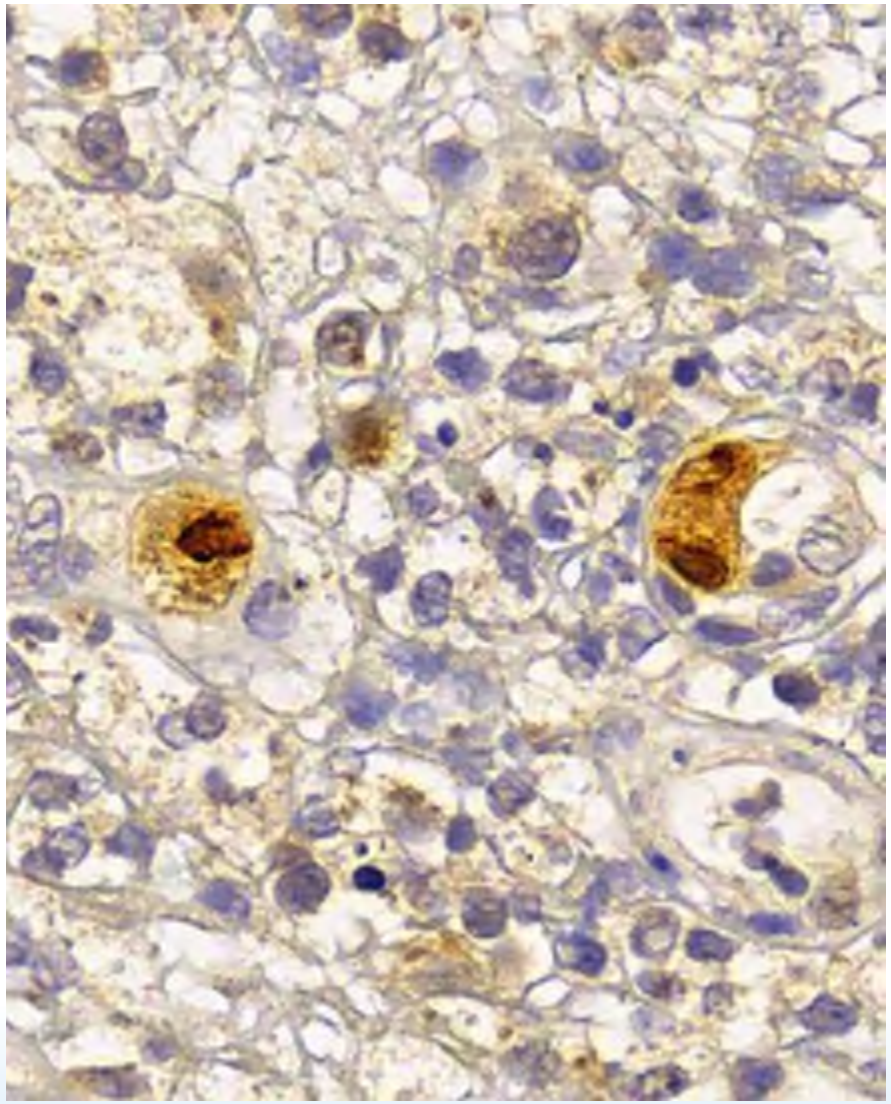


An abscess in an HIV infected man

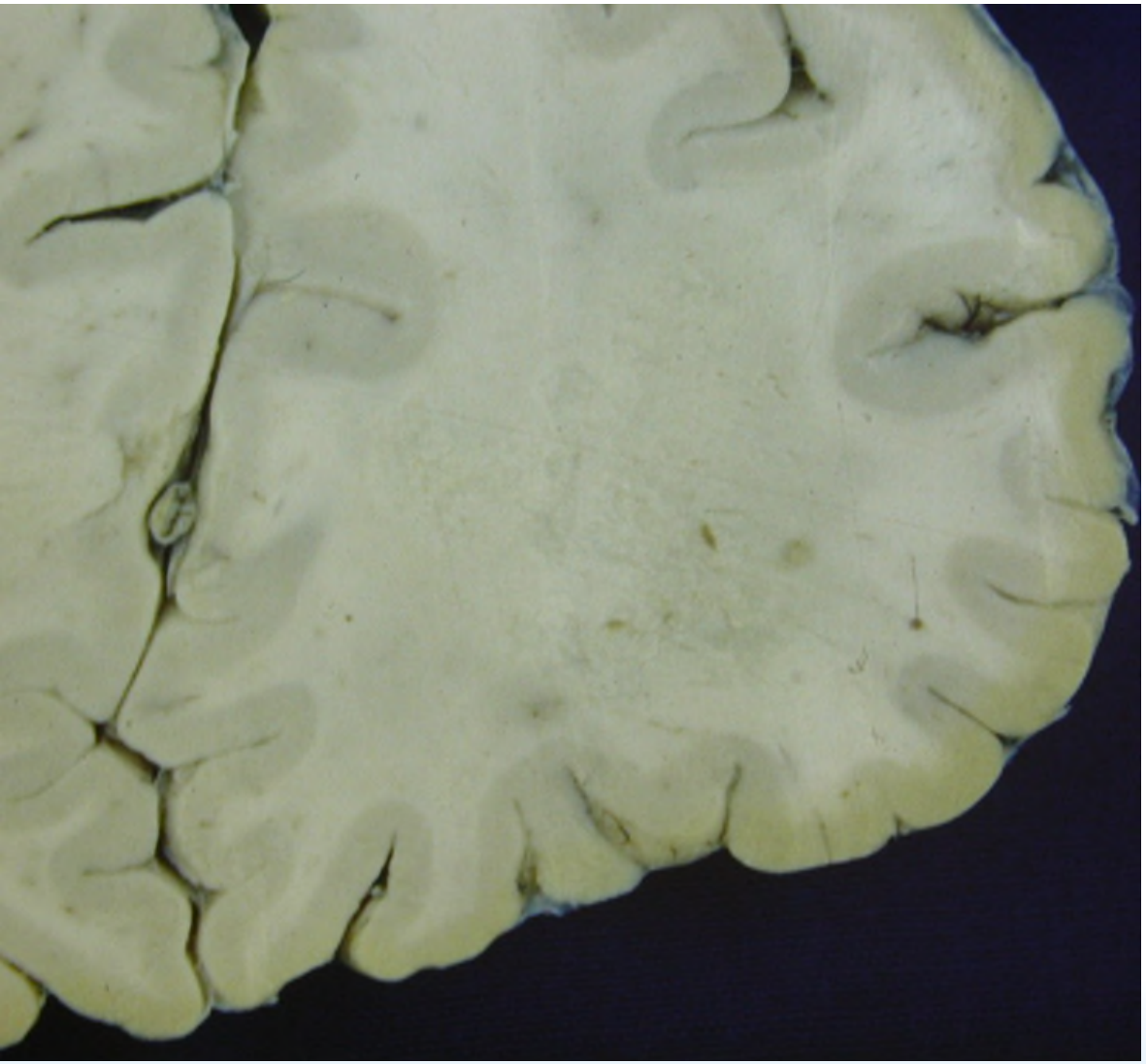


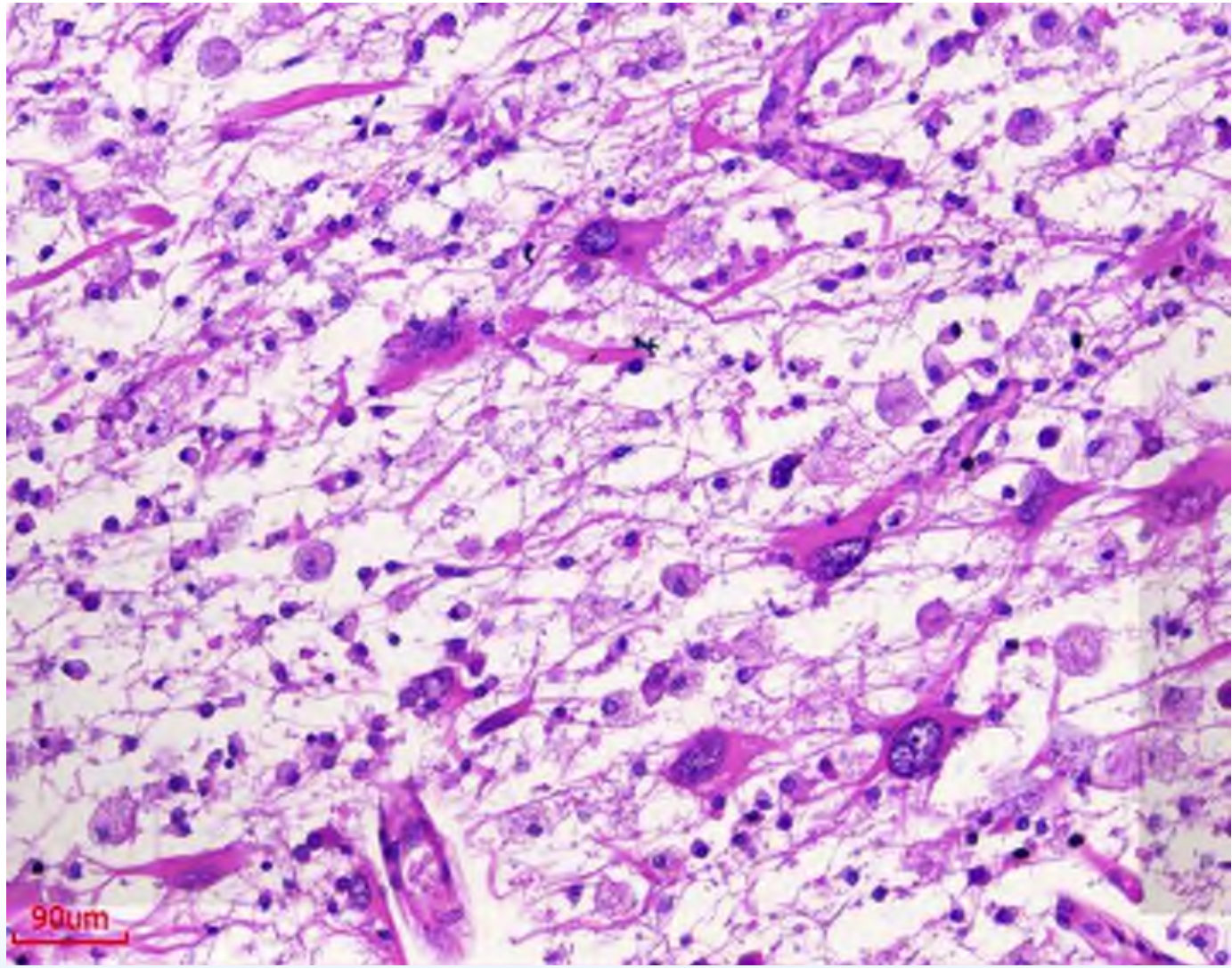




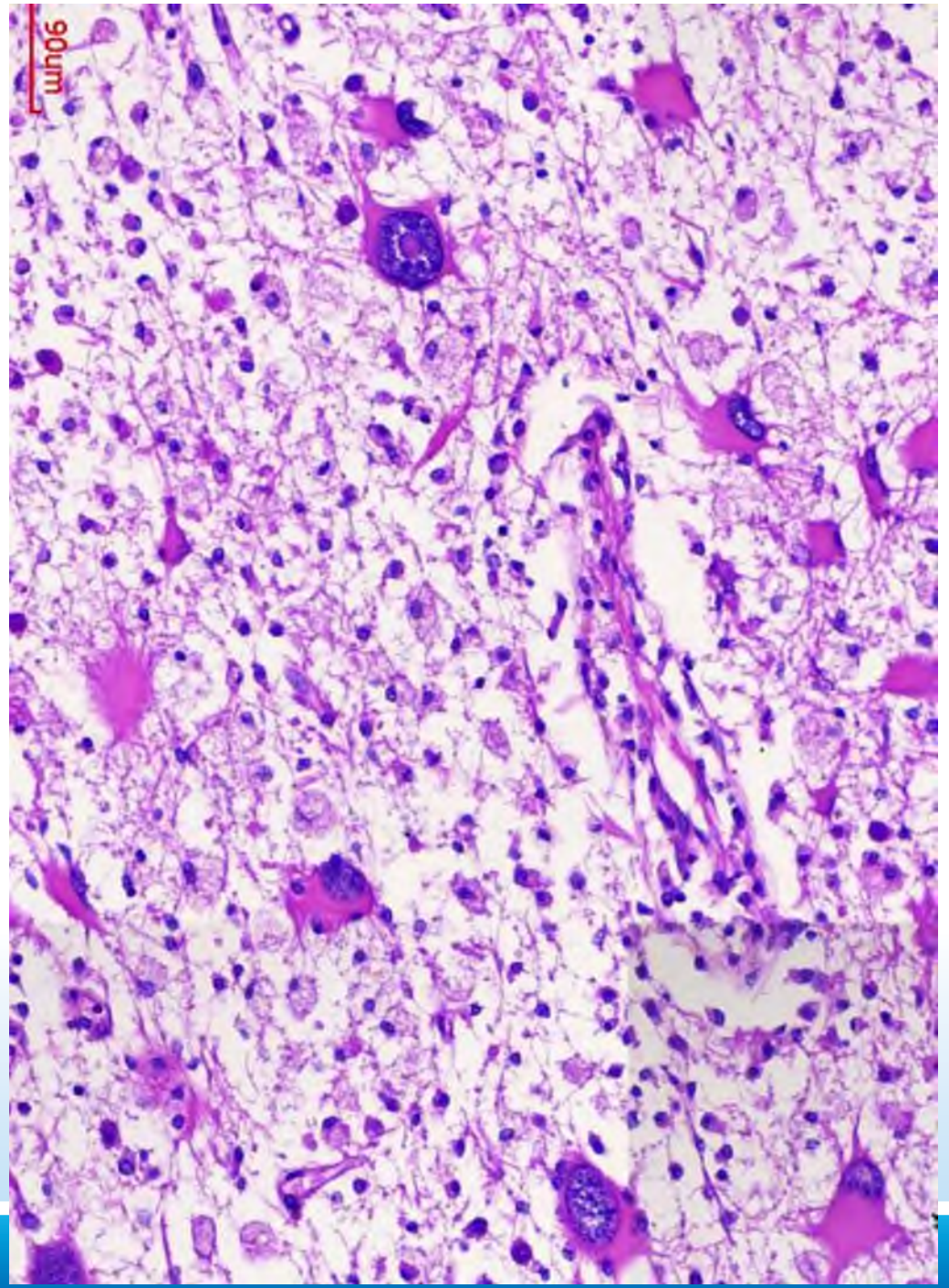


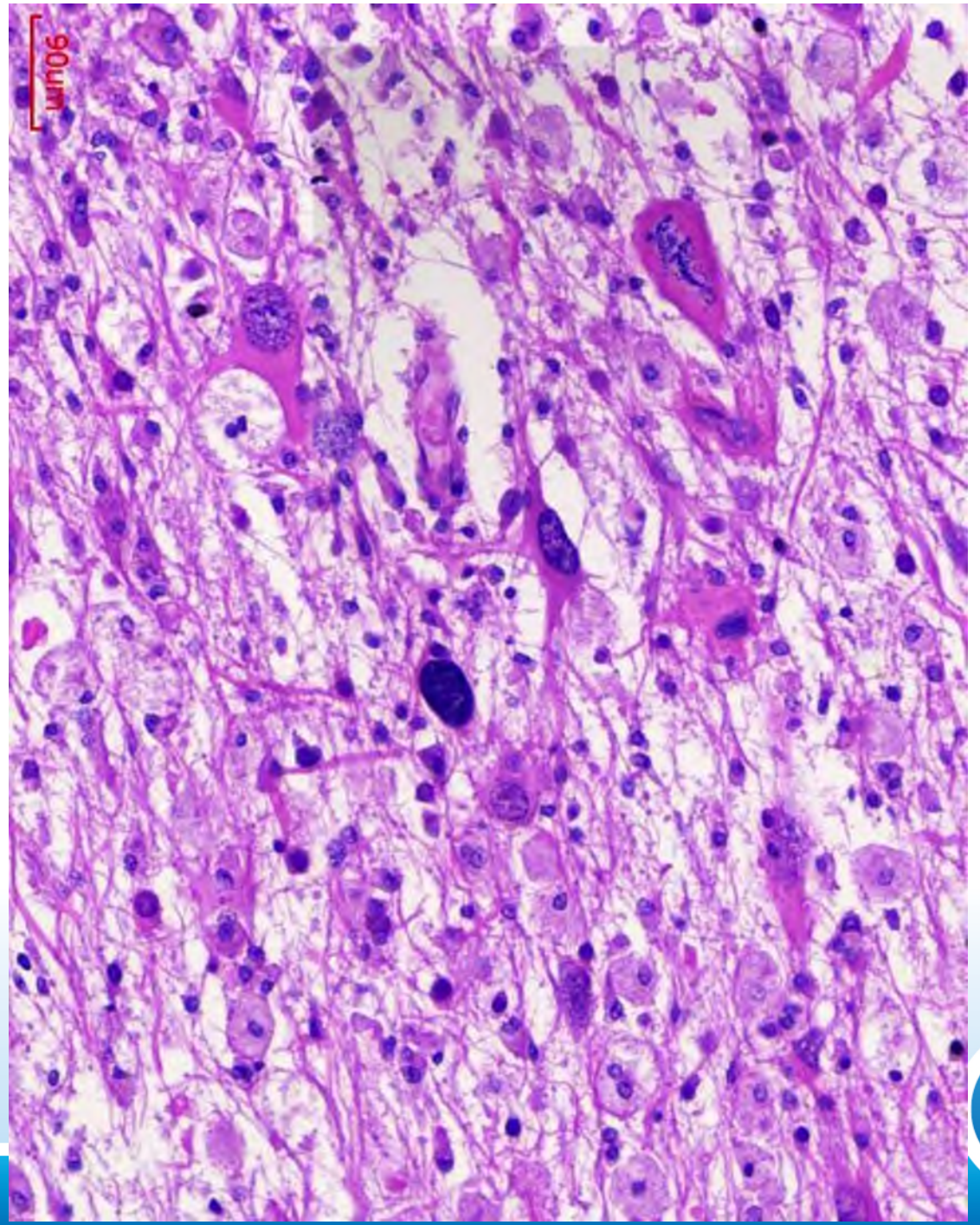
CMV (Herpes virus) may cause congenital encephalitis/vetriculitis/microcephaly,
but also myeloradiculopathy and (in this case) abscess in immunosupressed patients.



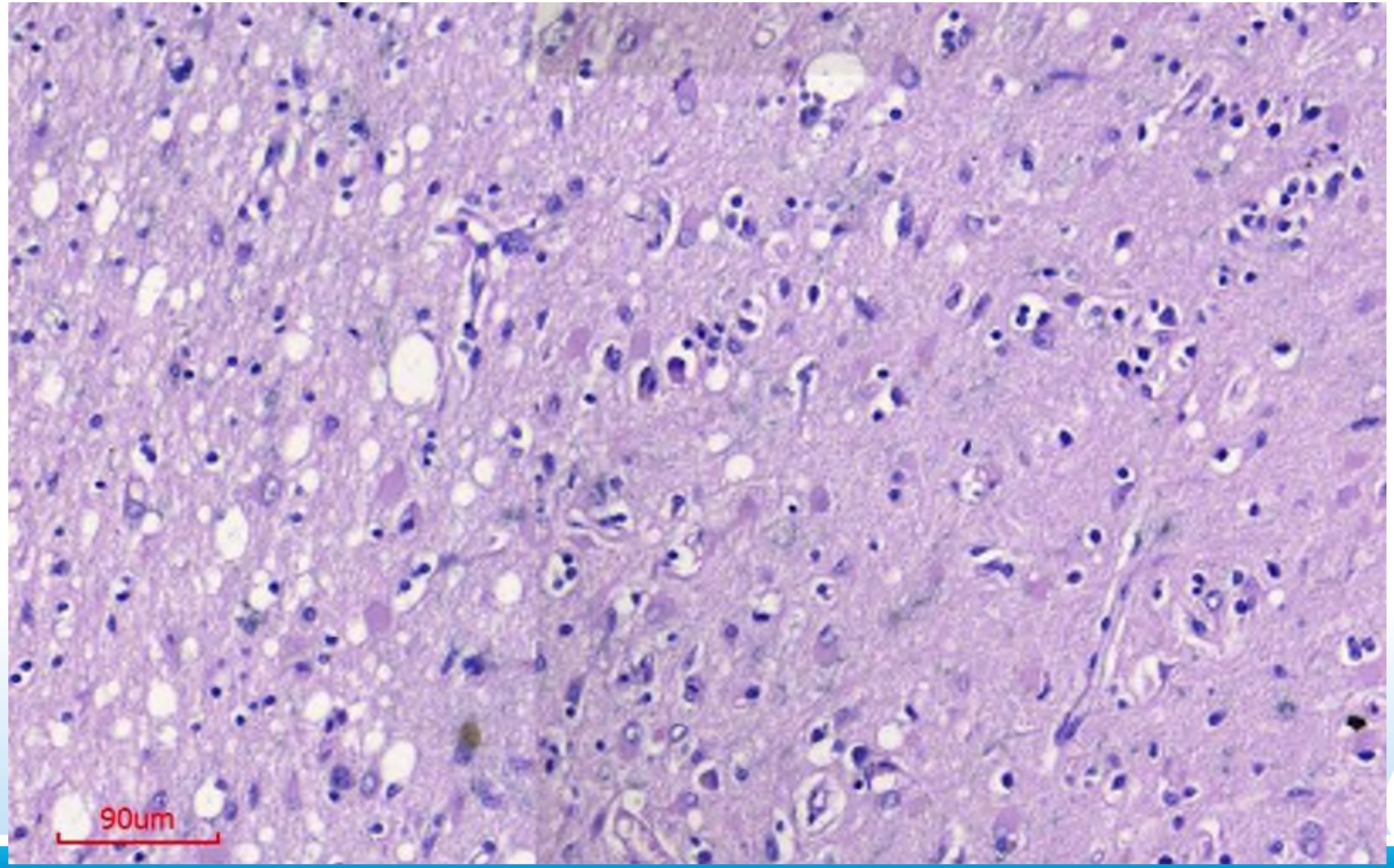


Progressive multifocal leukoencephalopathy - Polyomavirus – JC virus
Associated with immunosupression

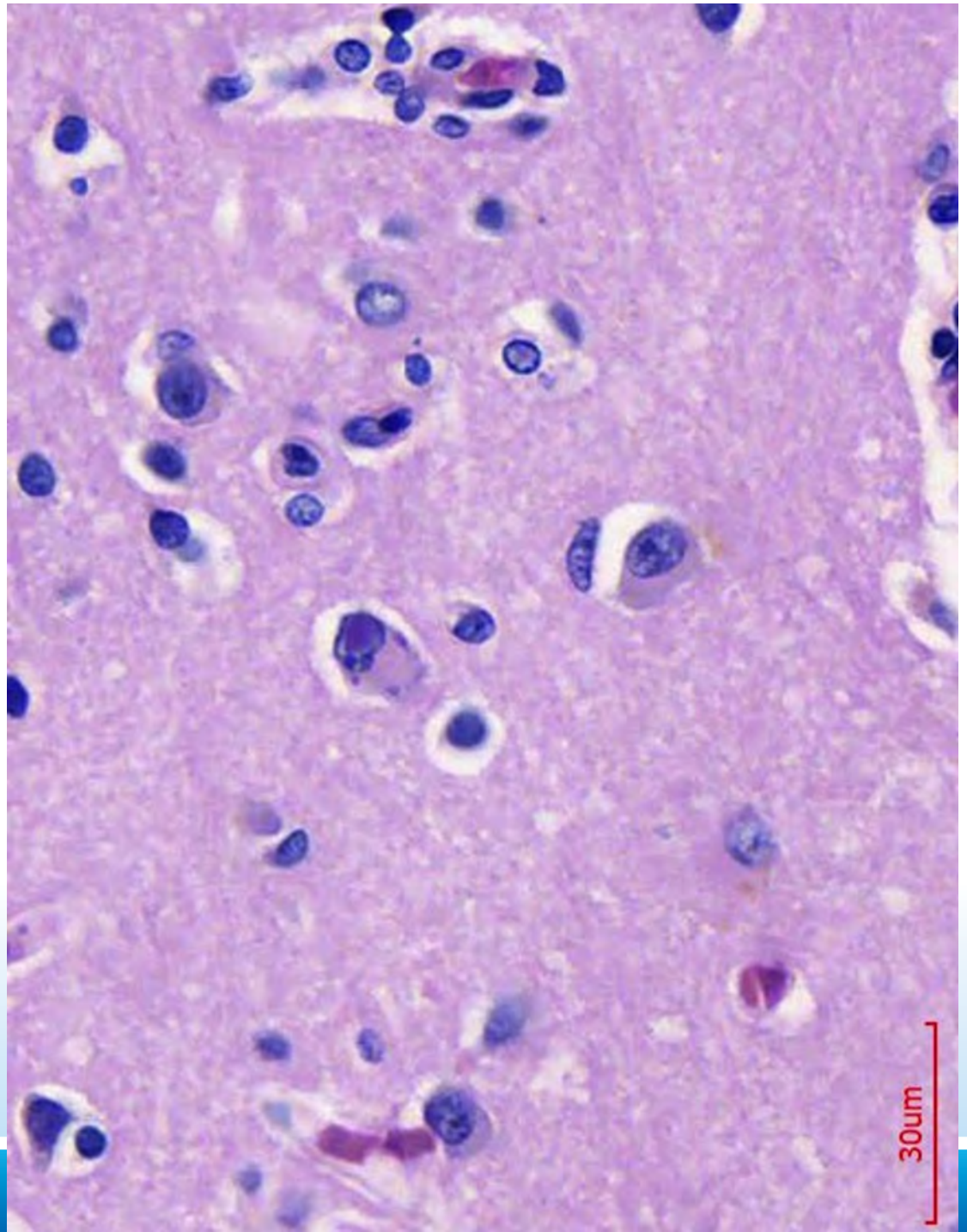

90um

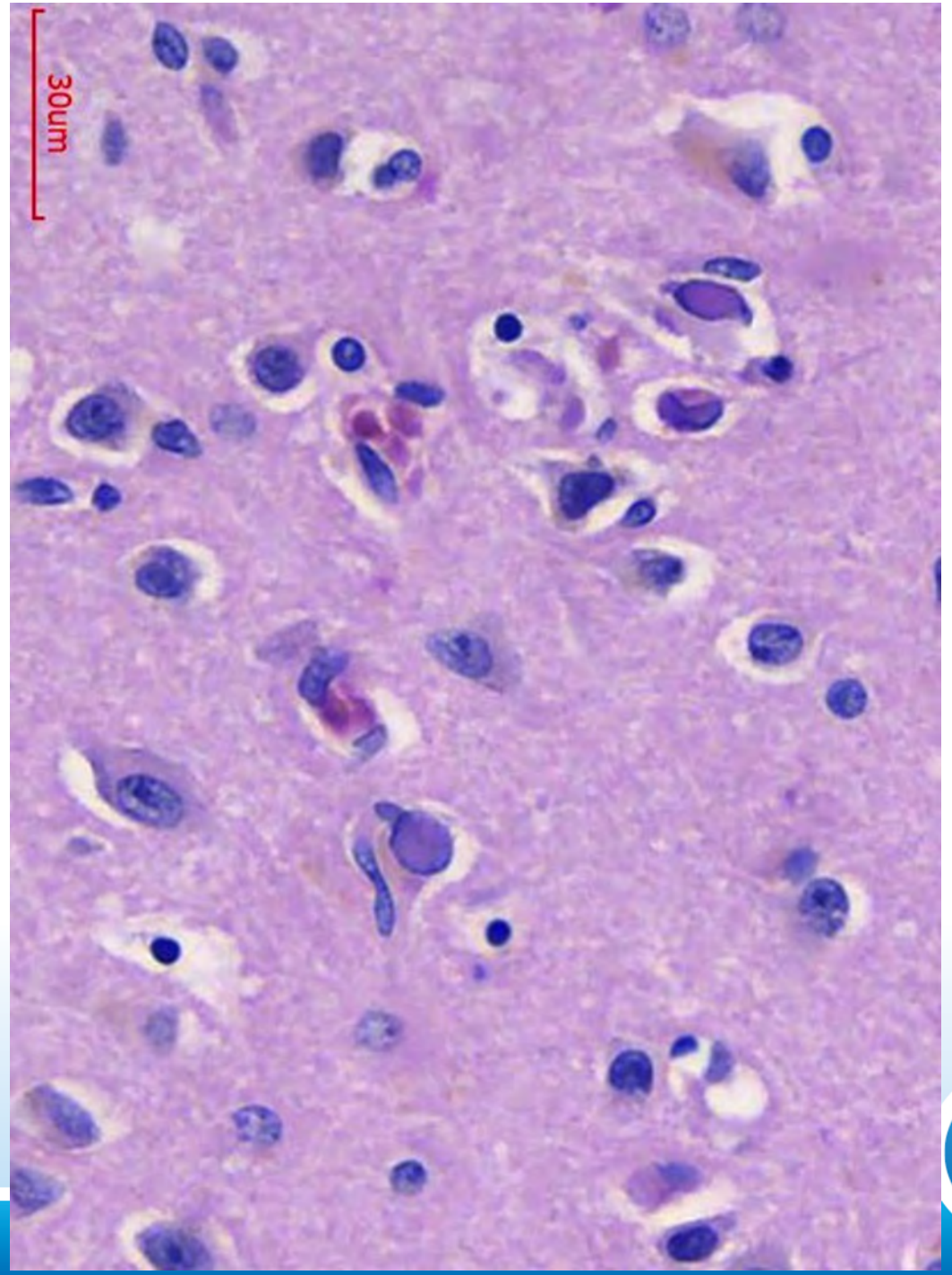

90um

34-year-old man who coursed with progressive dementia and myoclonus
Clinical hypothesis was prion disease




100um

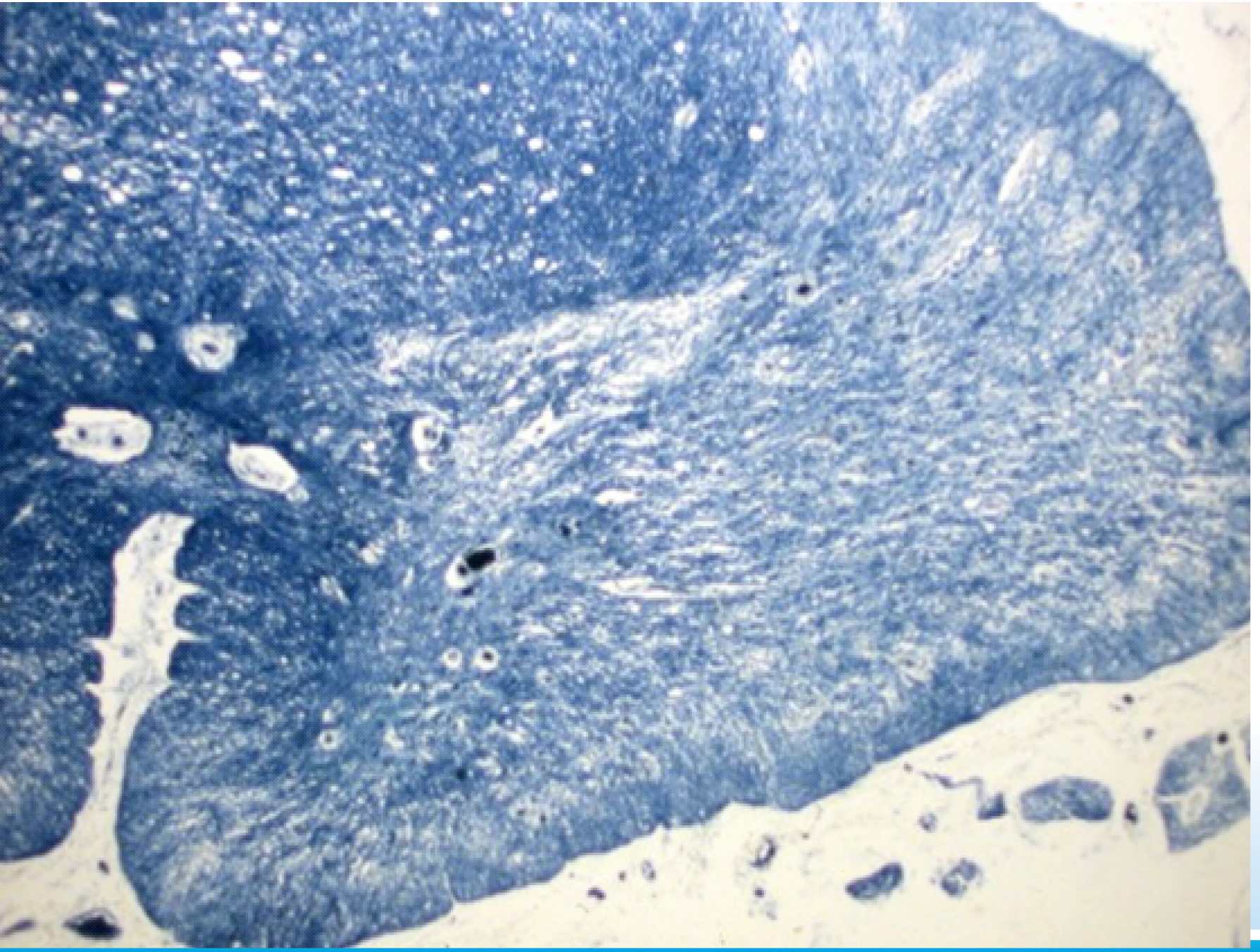




Diagnosis

SSPE

Post-measles



Retrovirus

HIV

HTLV1

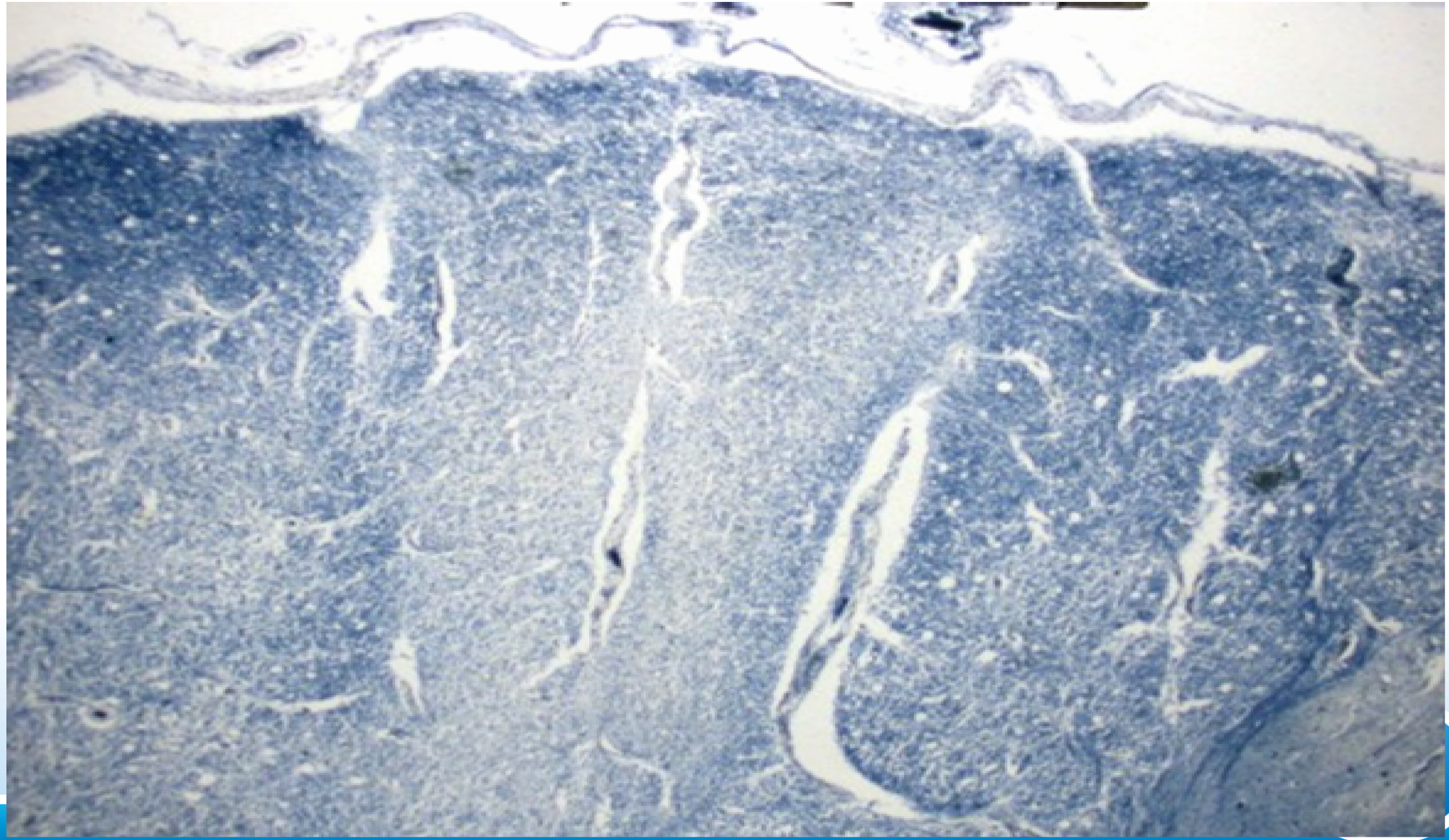
HTLV1

Myelopathy
Tropical Spastic Paraparesis

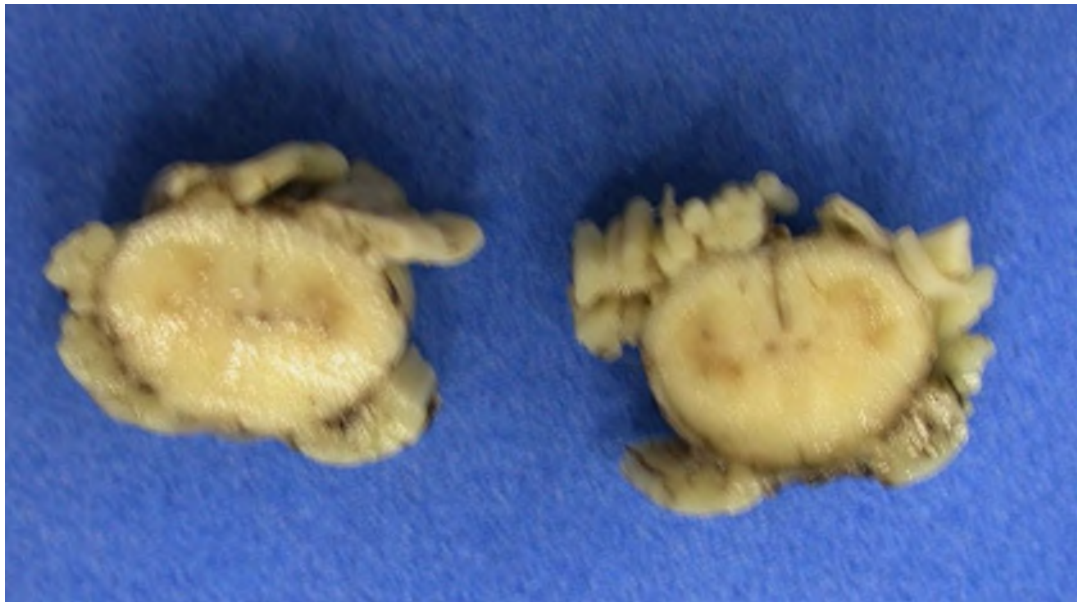
Affects descending and ascending tracts

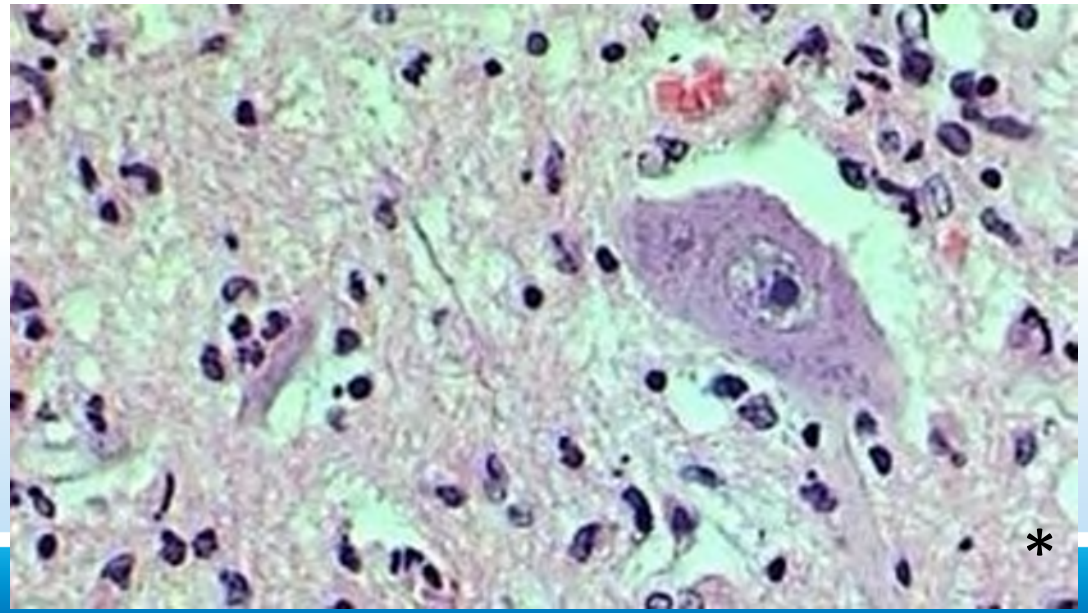
Degeneration of descending motor corticospinal tract

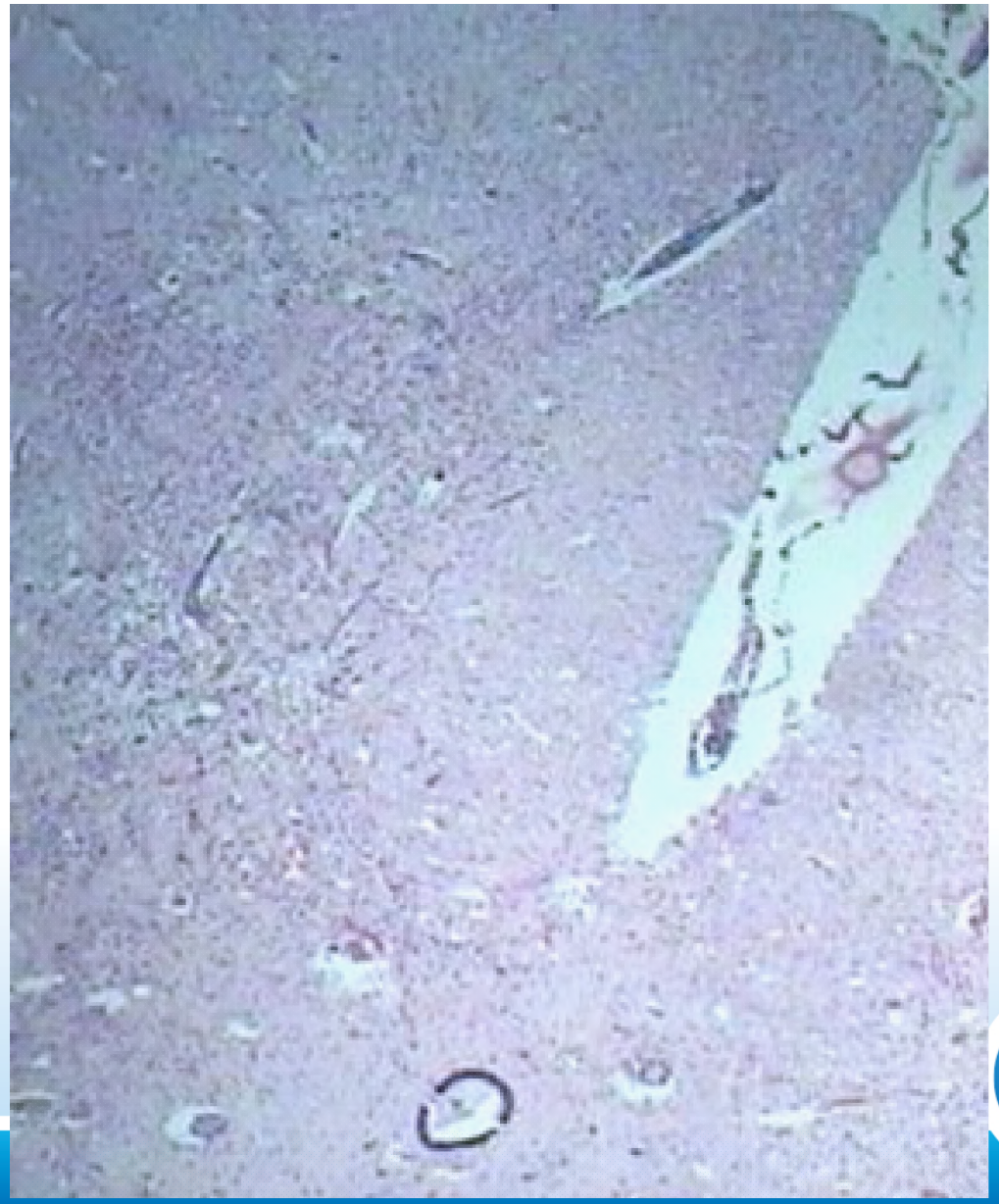
Degeneration of ascending sensory tract



Enterovirus - Poliovirus - Poliomyelitis -

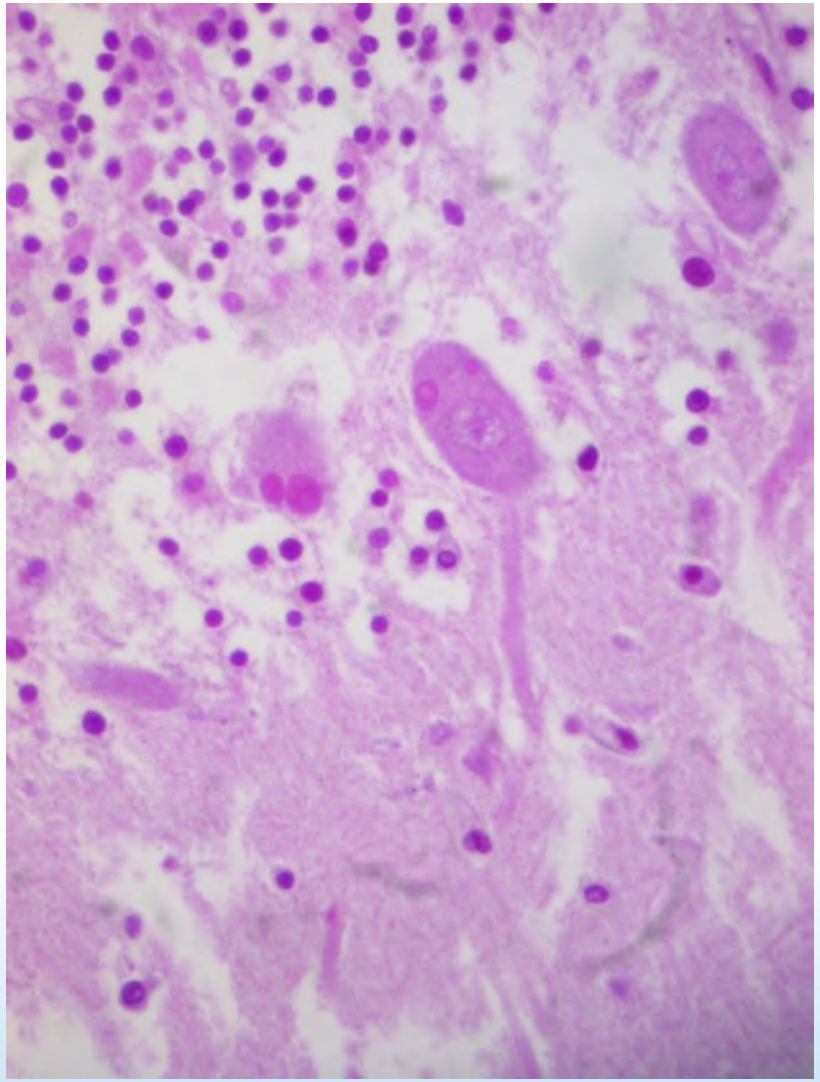


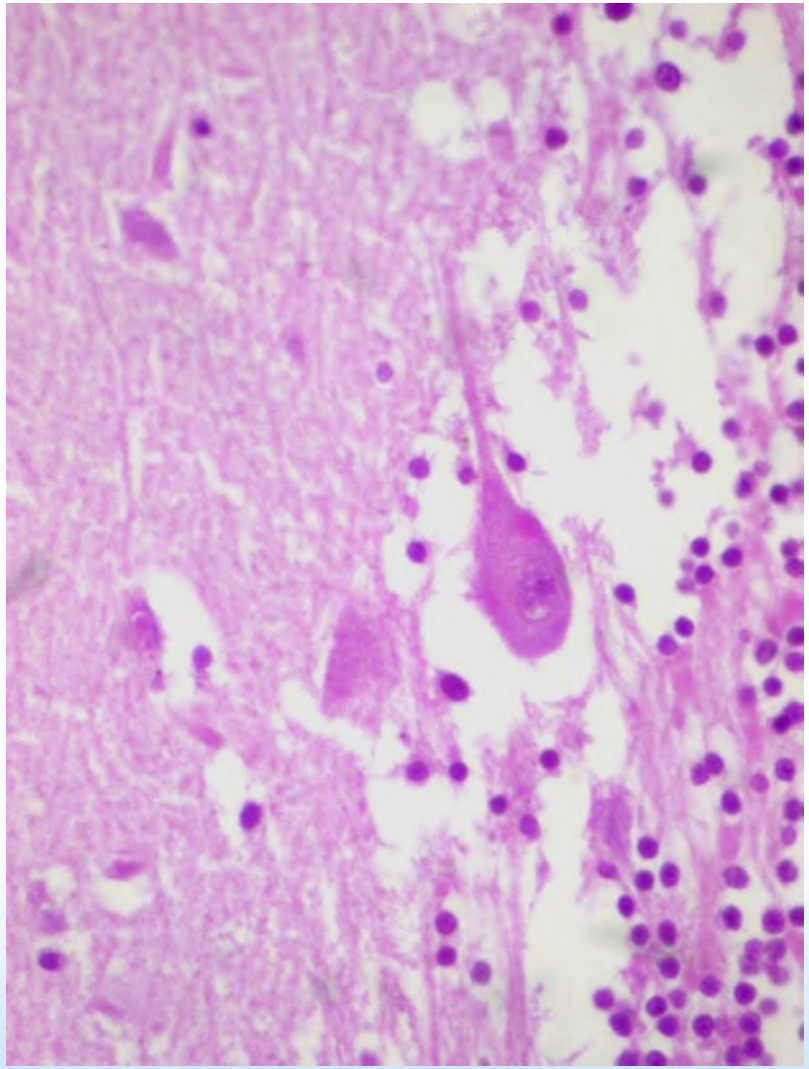




Rabies

Cytoplasmic eosinophilic inclusions in Purkinje cells - Negri bodies





Morphological Presentations of the Lesions

- Meningitis
- Encephalitis/Myelitis (Polio, Leuko)
- Encephalopathy/Myelopathy

- Space occupying lesions “Pseudo-tumors”
  - Abscesses
  - Granulomatous lesions
  - Non-granulomatous (necrotizing) lesions
  - Cystic lesions
  - Calcified lesions

- Vasculitis/Infarct/Hemorrhage
- Congenital infections / Malformations

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