

CENTRAL NERVOUS SYSTEM

INFLAMMATORY AND DEMYELINATING DISORDERS

APPROVED

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If she just read word for word, I didn't retype what she wrote. So if the slide looks sparse, it's bc she just read it.

- These diseases are rare.
- However, the bacterial diseases are very treatable if dx and recognized in a timely fashion.
- Fatal if not recognized!
- That's why they're important.

Objectives

- Recognize and describe the **pathology** of common inflammatory and demyelinating diseases of the CNS: bacterial infections, viral infections, fungal infections, HIV and infections associated with HIV, multiple sclerosis and central pontine myelinolysis
- Describe the **pathophysiology** of the common inflammatory and demyelinating diseases of the CNS

-This lecture will focus on the Pathology
-We will get details on the organisms in micro lectures.

CENTRAL NERVOUS SYSTEM INFLAMMATORY DISORDERS

- When evaluating a patient with inflammation and a possible infection of the CNS, it is important to consider the following:

These factors will help you ID the most likely organism

- **Anatomic compartment**

Is it in the scalp, skull, epidural space, subdural space, arachnoid and/or cerebrum?

- **Duration of symptoms**

acute onset and rapidly progressive?
indolent: developing and progressing over months?

- **Age of patient**

neonate? child? young adult? elderly?

- **Biological state of patient**

normal healthy adult? HIV/AIDS?
immunocompromised?

MENINGITIS

technically, dura mater part of meninges. But that's not included within meningitis.

- Inflammation of the meninges (arachnoid and pia).
- Clinical presentation is with
 - **Headache, vomiting, fever and stiff neck.**
 - **Seizures are common in children.**
 - **Symptoms are caused by inflammation of the meninges and the subarachnoid space. CSF fills this space.**

really rigid, not just a little stiff. cannot flex the head

so need to examine CSF for pathogen

MENINGITIS

- CSF abnormalities are present which vary with the organism.

– **Bacteria** cause a **neutrophilic reaction**, ↑ **protein**, ↓ **glucose**

lots of PMNs (polynuclear lymphocytes)

bc have inflammatory mediators, neutrophils, bacteria

bacteria eat up glucose

– **Encapsulated organisms** cause a **granulomatous reaction**, ↑↑ **protein**, **normal or ↓ glucose**.

like cryptococcus

may not be as metabolically active as bacteria

– **Viruses** cause a **lymphocytic reaction**, ↑ **protein**, **normal glucose**

bc obligate intracellular org. get nutrients from cell, not from glucose in CSF

T and B Cells

– **Syphilis** causes a **plasmacellular reaction**.

get lots of plasma cells

NEUTROPHILIC (BACTERIAL) MENINGITIS

Neonates - E. coli and Group B Streptococcus

Baby's brain. Died of E. Coli infection.

-Exudate in meninges. Not as much exudate as you'd see in adults. Why?

1. in neonates, immune system not totally developed and need less pathogen to cause severe morbidity/death.
2. Cannot put out as many inflammatory cells



Read the paragraph. Read the arrows when you get to that word.

Case History

pediatric patient with meningitis.

inadequately treated

fairly common problem in children

- 3 year male with a history of multiple middle ear infections developed fever and left ear pain. He was treated with Omnicef but developed vomiting and was unable to take his medication. He began IM injections. Fever and ear pain continued, his physician noted swelling and tenderness behind the ear and torticollis. CT demonstrated mastoiditis and an epidural abscess. MRI revealed a brain abscess. The abscess was drained and culture grew *Streptococcus pneumoniae*.

indicates infection is still present. need to reevaluate.

inflammation of the mastoid bone

majority of ppl she sees at autopsy with meningitis have strep pneumo. "So be careful of strep penumo"

wrenching of the neck

aka treated

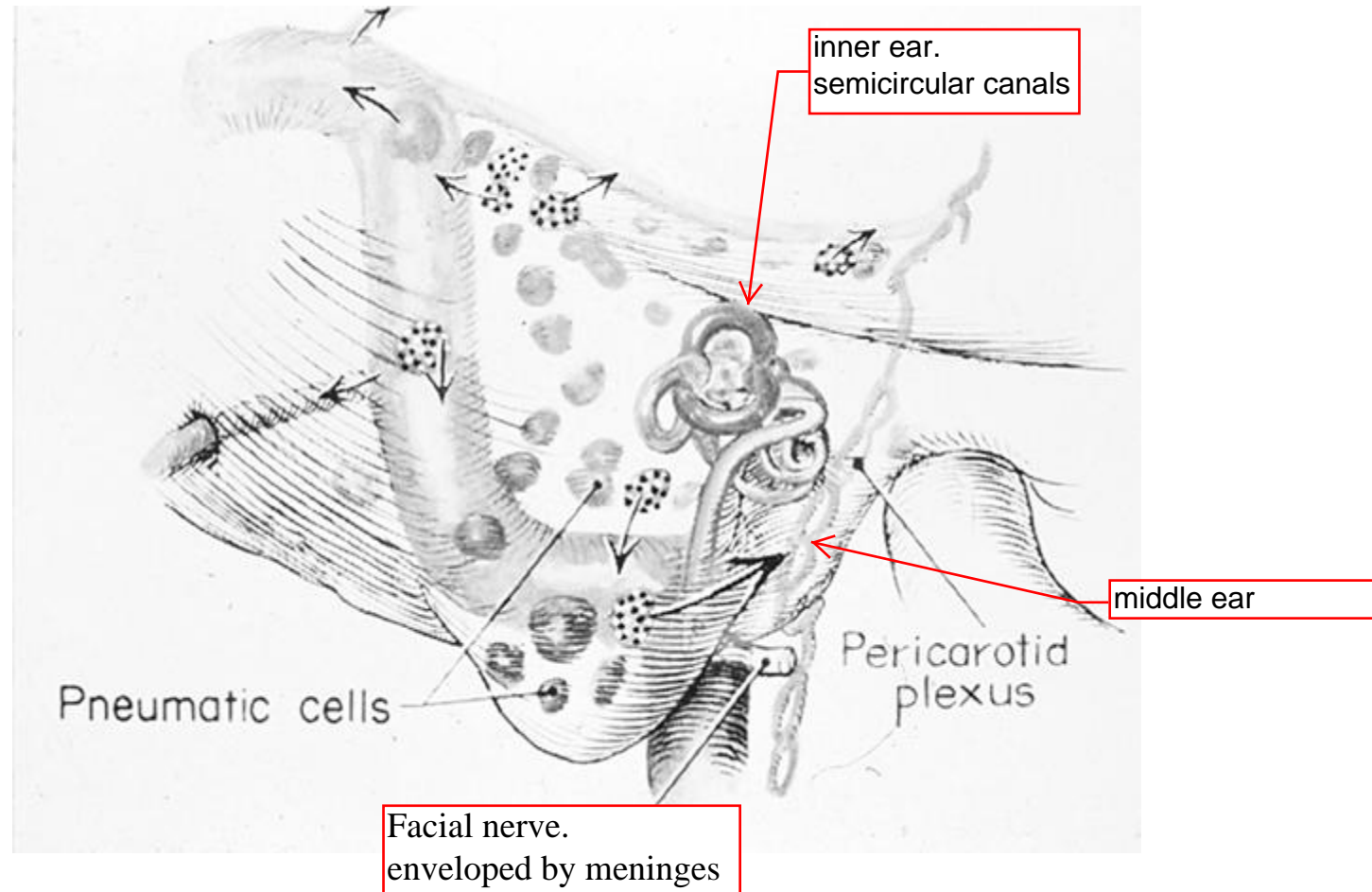
Success story! Kid went home and he was fine! :)

NEUTROPHILIC (BACTERIAL) MENINGITIS

MIDDLE EAR

How middle ear infection leads to meningitis.

Blood flow through bone, bacteria in ear can get into CNS. (she didn't elaborate beyond that)



NEUTROPHILIC (BACTERIAL) MENINGITIS

Streptococcus pneumoniae

pus (white stuff)



-patient who died of strep pneumo meningitis.

-compared to neonate in other slide:

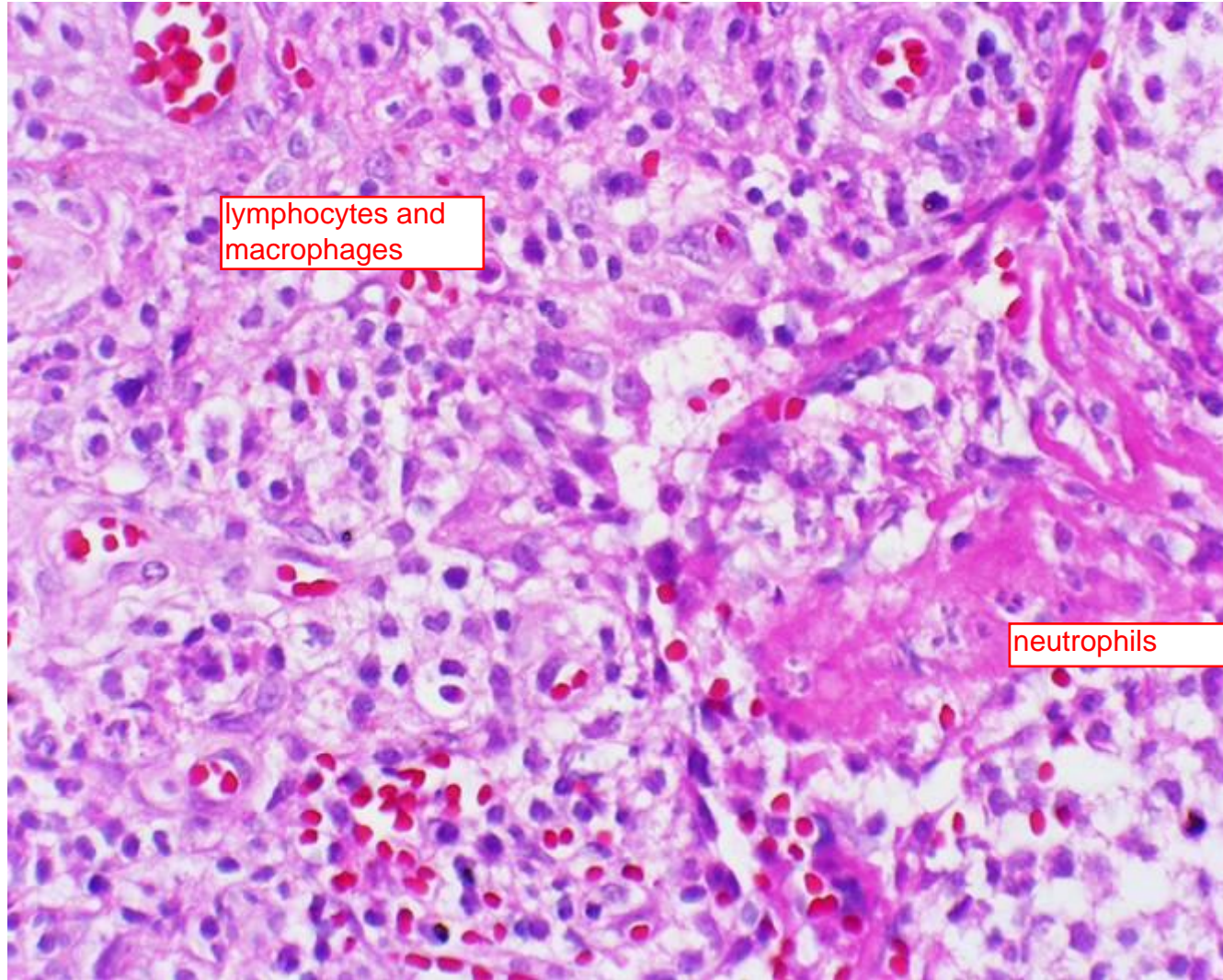
1. a lot more pus on the surface.

2. more vascular congestion

3. more exuberant inflammatory response

histological picture of brain abscess described on slide 7.

1. acute inflammatory cells (neutrophils) but also chronic element (mononuclear cells) bc going on for a while



CEREBRITIS

if not treated, progresses to cerebritis:
florid bacteria infection of the brain

child. maintained on cardiorespiratory support
for a while, so progressed to a point where
you virtually have necrosis of entire cerebrum



NEUTROPHILIC (BACTERIAL) MENINGITIS

Neisseria meningitidis



causes epidemic meningitis, particularly in young adults in close quarters(dorms, army)
-very contagious.
-very aggressive
-milky white inflammatory infiltrate in meninges

It is very important to note that
marked individual variation
occurs.



Remember this!

-N. meningitis could also occur in elderly, not just young adults.

-Strep pnemo can be seen in everybody, not just young child.

The examples cited here are
guidelines only.

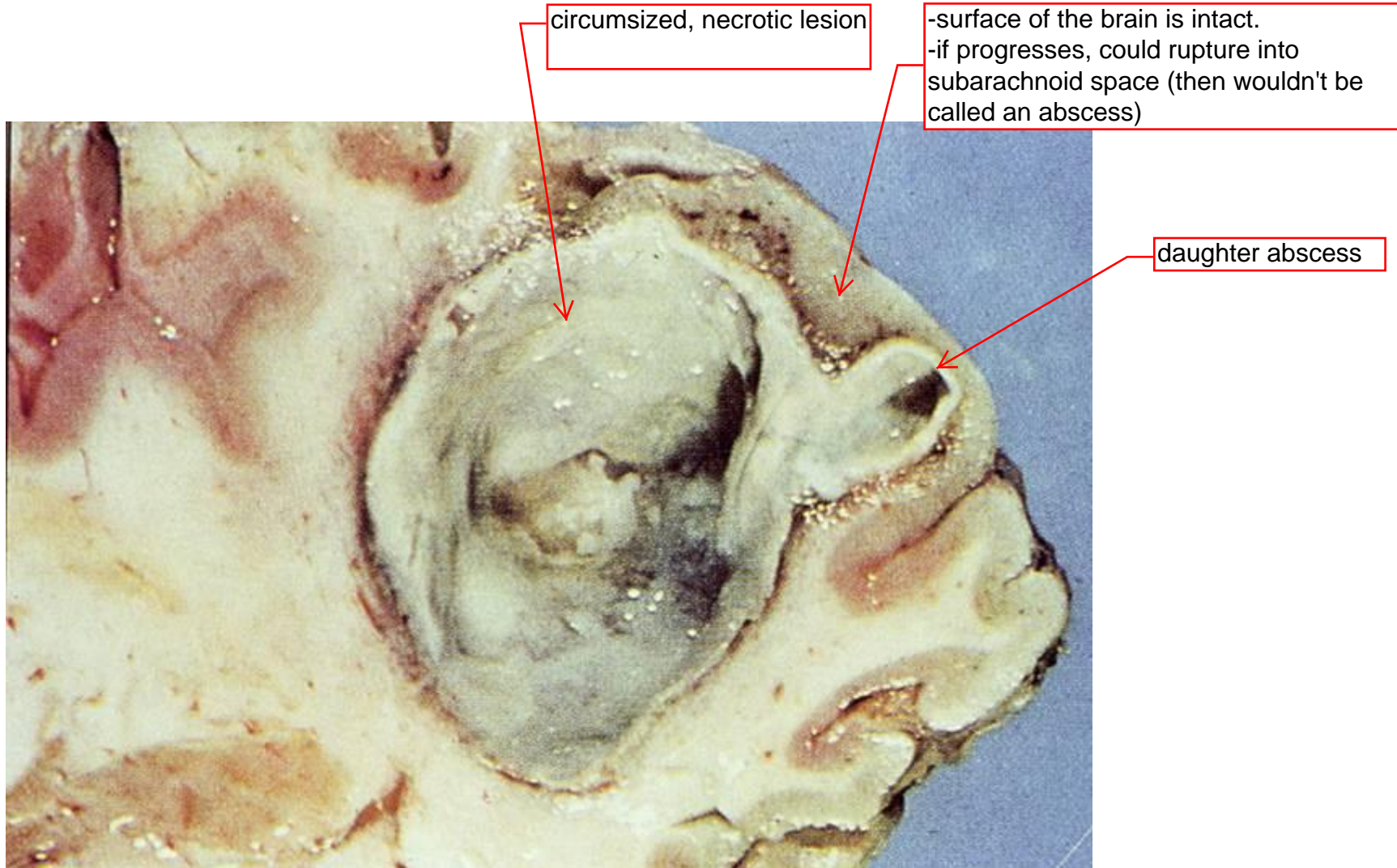
Question: Since CSF drains into spinal canal, would you also get infection/equal inflammation in the spinal cord?

YES, YES, YES! Always when you have meningitis. That's where we get CSF fluid to test for infection-spinal tap in lumbar region (cauda equina region)

ACUTE FOCAL SUPPURATIVE INFECTIONS

- **Brain Abscess** This is a tumor: swelling in the brain. So see signs you would see with neoplasm in the brain.
 - **Clinical presentation is with focal neurological signs and raised intracranial pressure.** based on where it's located
bc mass lesion in the brain
 - **↑CSF pressure, WBC and protein & Glucose normal** all normal bc this is a confined process
- **Subdural empyema** very very uncommon. can occur as complication of inadequately tx meningitis, penetrating injury, surgical complication
- **Extradural abscess**
 - **Osteomyelitis** infection of the bone
 - **Surgical complication** these are both reasons you could get an extradural abscess

CEREBRAL ABSCESS



ACUTE ASEPTIC (VIRAL) MENINGITIS

- Usually a benign illness of children and young adults.
- There is CSF lymphocytosis, moderate ↑protein
- Most common viruses
 - **Coxsackie virus**
 - **Echo virus**
 - **Nonparalytic polio virus**

usually resolve with symptomatic treatment and support.

CHRONIC BACTERIAL MENINGITIS

Mycobacterium tuberculosis

- Organisms gain access to the CNS via blood stream.
- Caseating granulomas form in the basal meninges.
- Parenchymal spread of infection results in a “tuberculoma” which may be mistaken for a tumor. the brain substance itself
- The infection is indolent but fatal in 4 -6 weeks if it is untreated. slowly progressive

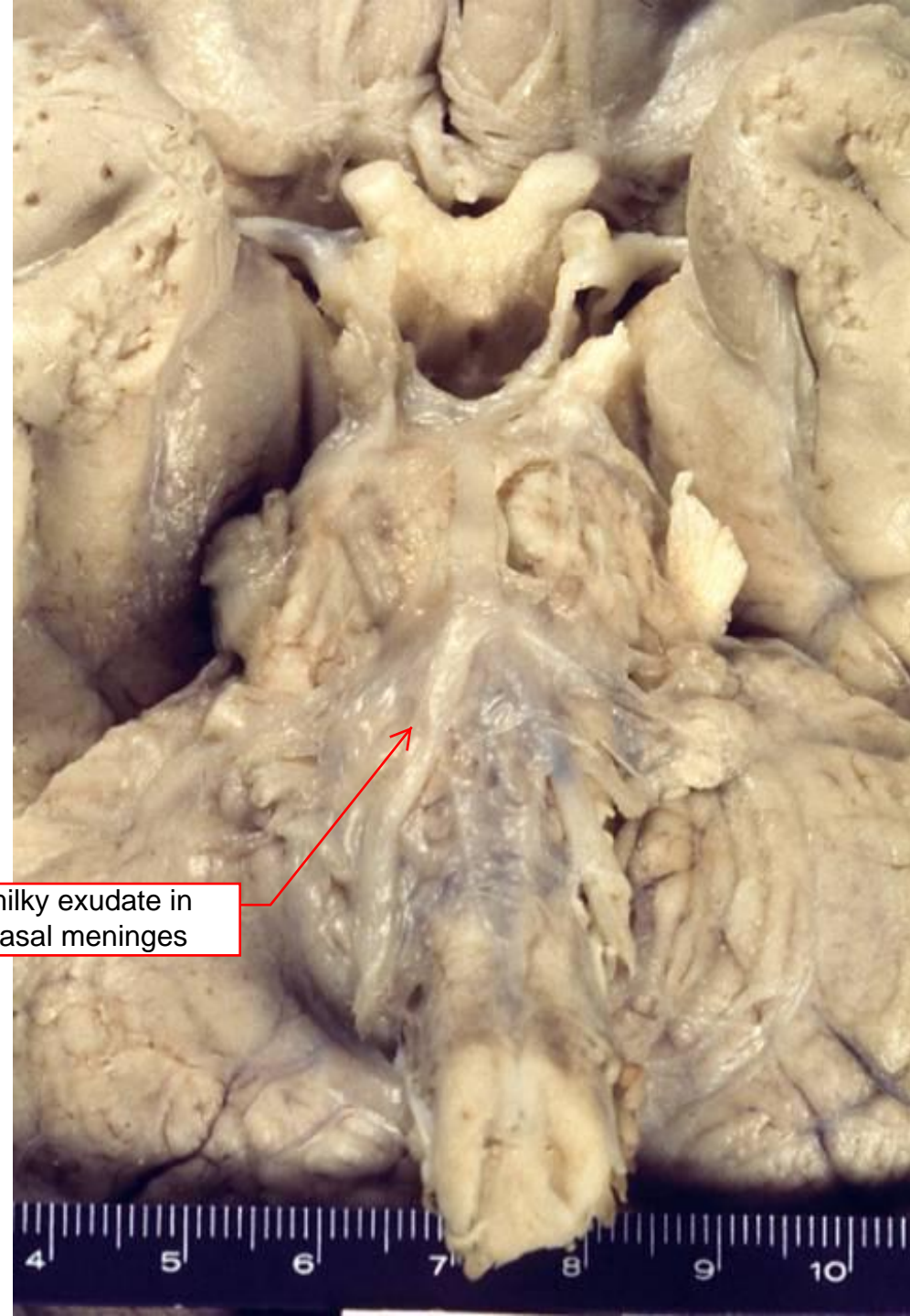
This was a little unclear. The slide says "May be mistaken for a tumor" but she said a tuberculoma "is a tumor," specifically a "-nitis of granulomatous inflammation and proliferation of the mycobacterium. "

My take is that on the slide, "tumor" is referring to neoplasm (aka cancer) but it is a tumor based on her previous definition of tumor as "a swelling in the brain"

The term tumor is derived from the Latin word for "swelling". However, in medical usage the term "tumor" is considered synonymous with neoplasm. Entymologically, a tuberculoma is actually a tumor. But in medical terms it is not.
Dr. H 2013

CHRONIC BACTERIAL MENINGITIS

*Mycobacterium
tuberculosis*

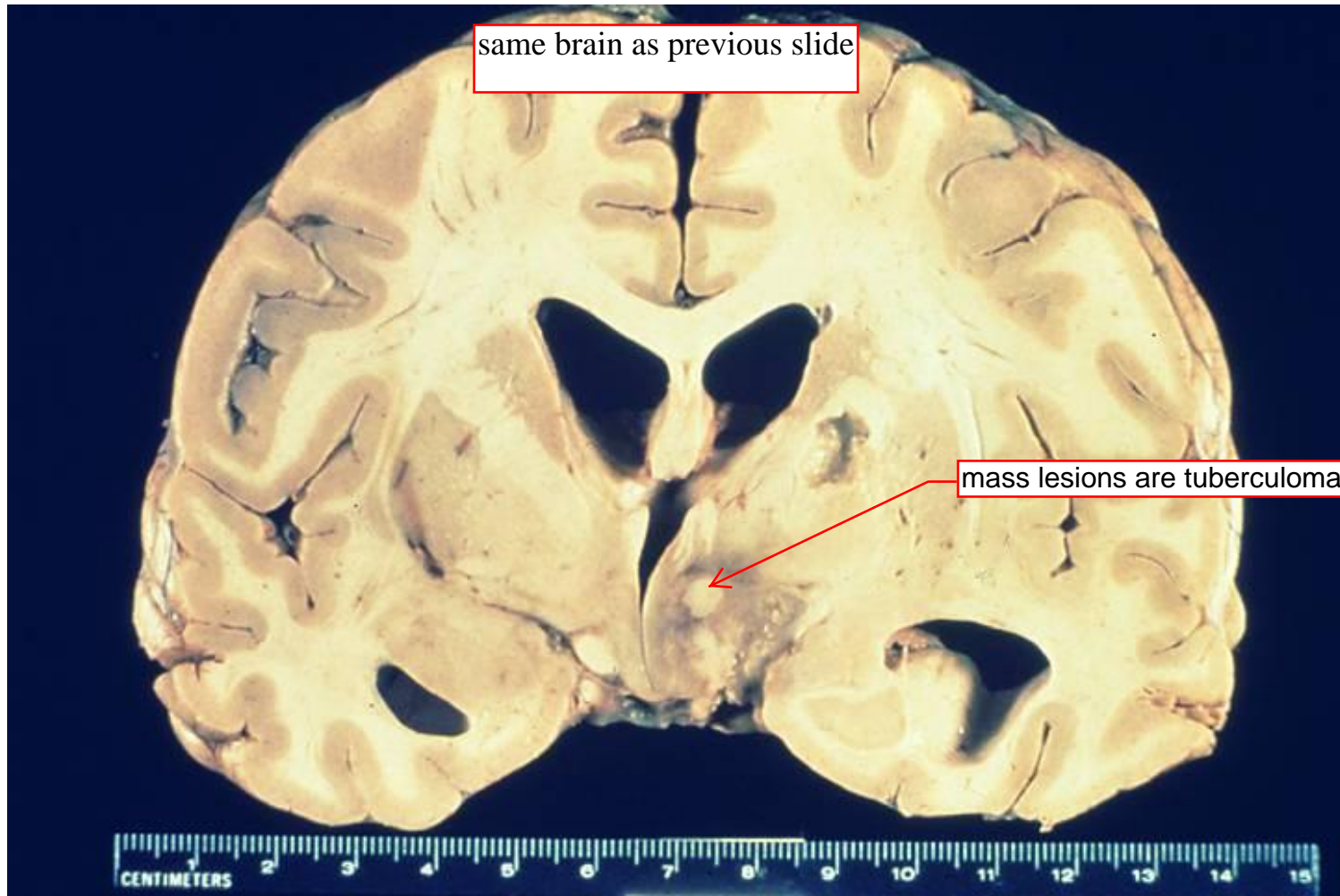


milky exudate in
basal meninges

CHRONIC BACTERIAL MENINGITIS

Mycobacterium tuberculosis

“Tuberculoma”

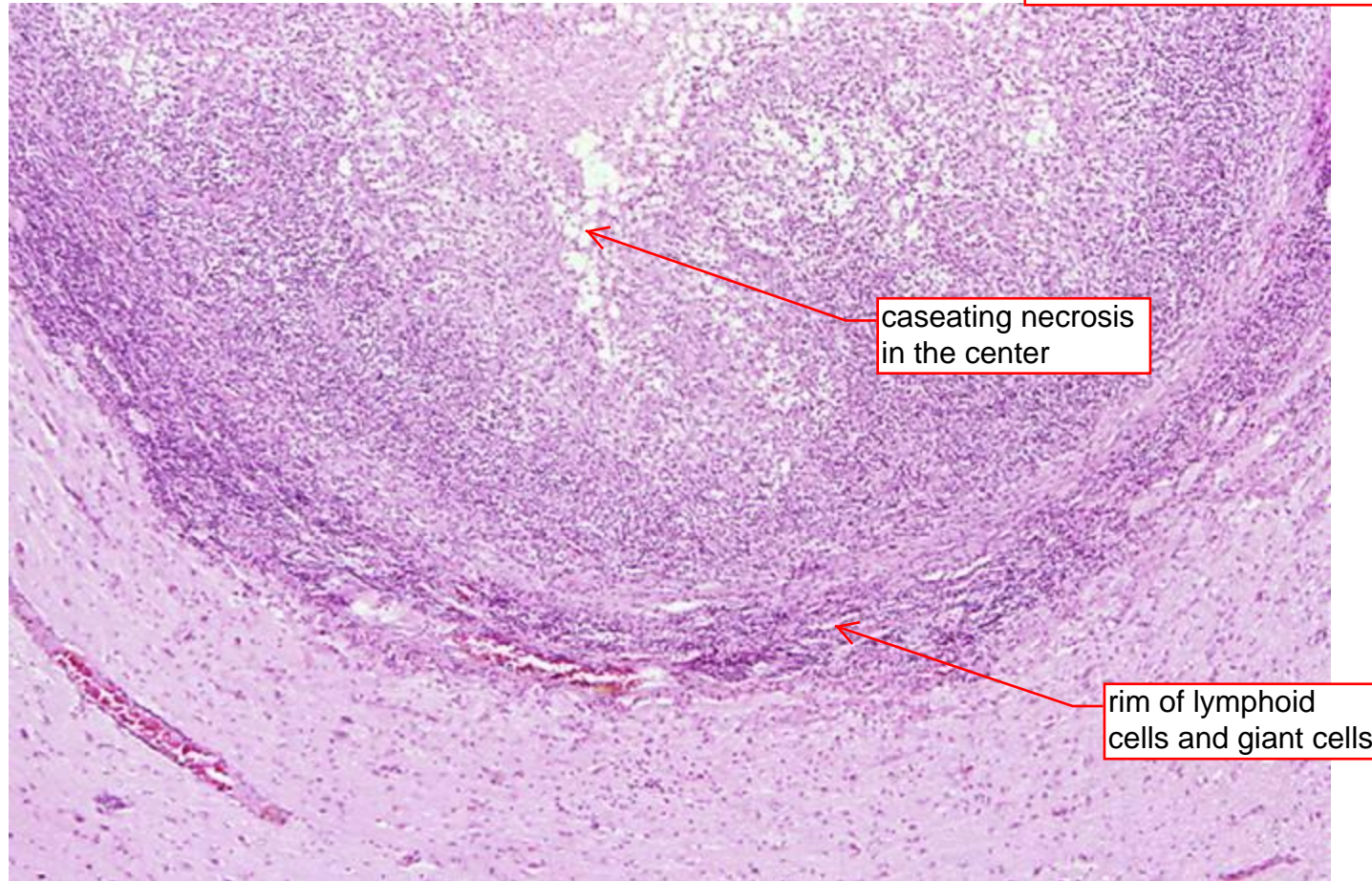


CHRONIC BACTERIAL MENINGITIS

Mycobacterium tuberculosis

Caseating granuloma

same as ones you'd see in the lung with TB infection, these are just in the brain!





POTT'S DISEASE

Before good tx for TB, this was a fairly common complication of TB. Not so much anymore bc we have effective tx available

(TB of the spine)

*Mycobacterium
tuberculosis*

CHRONIC BACTERIAL MENINGITIS

Treponema pallidum

SYPHILIS

rarely occurs bc very very sensitive to penicillin, so if you get penicillin for any reason it will knock out organism.

Concern of emerging problem in AIDS patients

- Neurosyphilis is the **tertiary stage** of syphilis and occurs in about 10% of patients with untreated infection. Three types of neurosyphilis may occur.
 - **Meningovascular neurosyphilis**
 - Chronic meningitis **plasma cellular inflammatory infiltrate**
 - **Paretic neurosyphilis**
 - Invasion of the brain causing dementia and other symptoms.
 - **Tabes dorsalis**
 - Inflammation of the Dorsal Roots causes impaired joint position sense and loss of pain sensation which leads to joint damage (Charcot joints)


this was common back in the 19th century. not so much any more with penicillin

Which of the following statements about meningitis is/are true?

- A. May be acquired via the blood stream
- B. May be acquired by direct implantation (surgery or trauma)
- C. May be acquired by local extension of an abscess
- D. May be rapidly fatal if not diagnosed and treated
- E. All of the above

VIRAL MENINGOENCEPHALITIS

infection (itis) of meninges (meningo) and the brain itself (enceph)

- Most commonly caused by Arboviridae.
 - **Eastern and Western equine, Venezuelan, St. Louis and La Crosse most common in US** these are types of arboviridae
- Virus is transmitted by mosquitoes and ticks. transmitted by insect bites
- Clinical features vary with the virus and the immunocompetence of the host
- Pathology varies from mild meningitis to severe encephalitis.  debilitating, deadly
- Perivascular and parenchymal mononuclear infiltrate and microglial nodules

Question about West Nile Virus...we will talk about this in micro ID lecture, she's not going to talk about it now

VIRAL ENCEPHALITIS

you can take nice pictures of them so they show up on tests

INCLUSION FORMING VIRUSES

- These diseases are generally less common but they are important diagnostic considerations.
- Herpes viruses
 - Herpes simplex
 - Herpes zoster
 - **Cytomegalovirus**
- Rabies
 - Rhabdovirus, **Negri bodies**
- JC virus
 - **Progressive multifocal leucoencephalopathy**
- Measles virus
 - **Subacute sclerosing panencephalitis**

path feature associated with Rhabdovirus infection

in AIDS population

very rare, rare, rare complication of measles

VIRAL ENCEPHALITIS

Herpes Viruses most common causes of viral encephalitis

- HSV-1 causes “cold sores”.
 - Virus resides latent in the trigeminal ganglion.
 - Reactivation may cause Herpes encephalitis which is necrotizing and localized to the temporal lobes. very rare complication
tx with antivirals
- HSV-2 infects infants via birth canal thus, do C-section if mom has genital herpes
 - It also causes a necrotizing encephalitis.
- Herpes zoster (Shingles) affects older adults
 - Reactivation of chickenpox (Varicella) infection.
 - Causes a radiculopathy.
- Cytomegalovirus
 - Causes encephalitis in fetuses infected in utero and in immunocompromised adults, especially AIDS patients.

VIRAL ENCEPHALITIS

Herpes simplex



necrotizing reaction localized to the temporal lobes

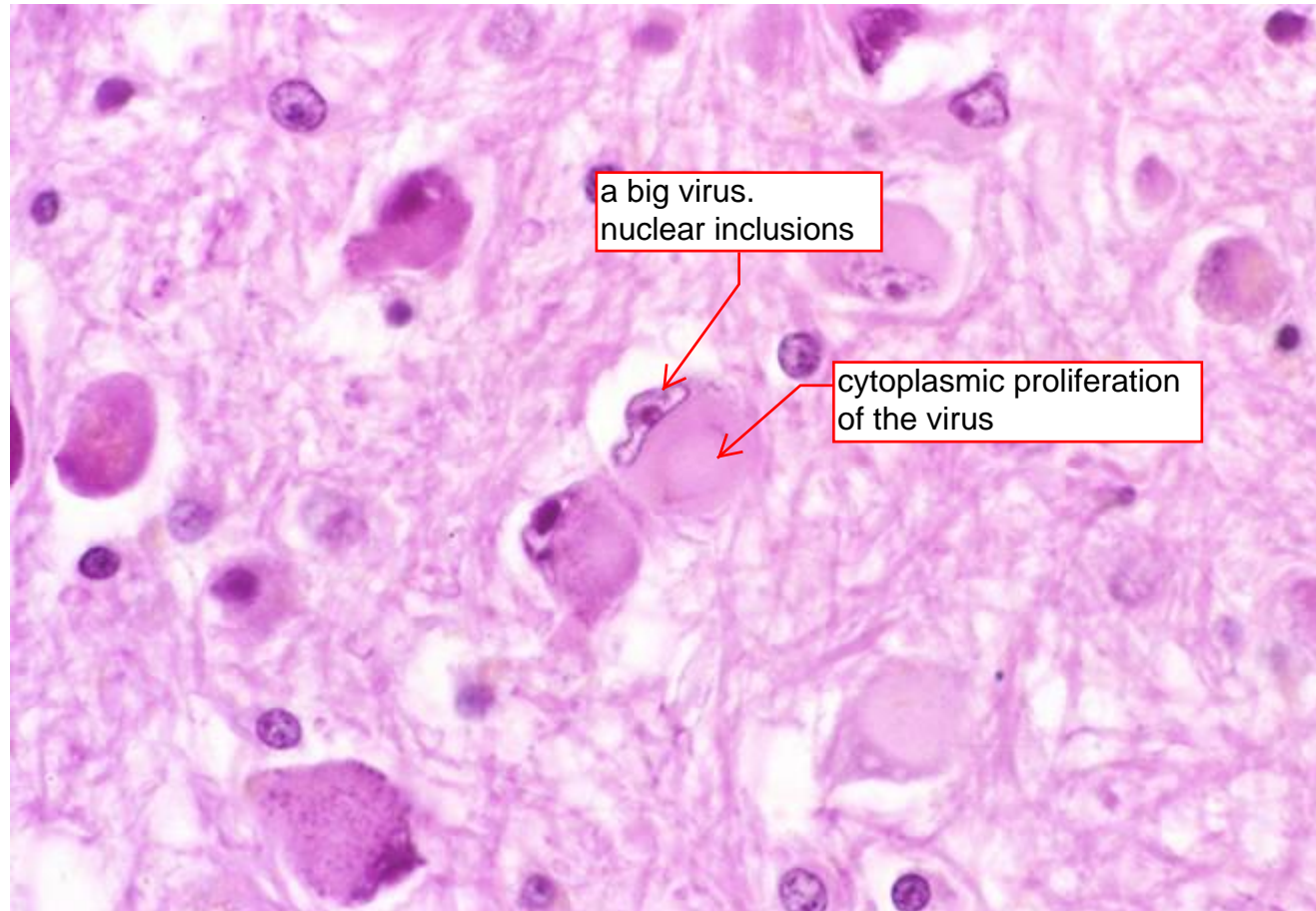
VIRAL ENCEPHALITIS

Herpes simplex



VIRAL ENCEPHALITIS

Cytomegalovirus



VIRAL ENCEPHALITIS

Rabies

- Rhabdovirus
 - **Enveloped ssRNA**
- Transmitted from saliva
 - **Dogs, wolves, skunks, foxes are animal reservoir.**
 - **Exposure to bats without a bite may result in disease.**
 - **Latent period is 10 -90 days.**
- Virus travels via peripheral nerve → spinal cord → brain.
- Destruction of brain stem neurons causes “hydrophobia”.
- Negri bodies are pathognomonic cytoplasmic eosinophilic inclusions in pyramidal neurons.

bit on toe=longer latent period than if bit on arm

spelunkers. transmitted in secretions without bite

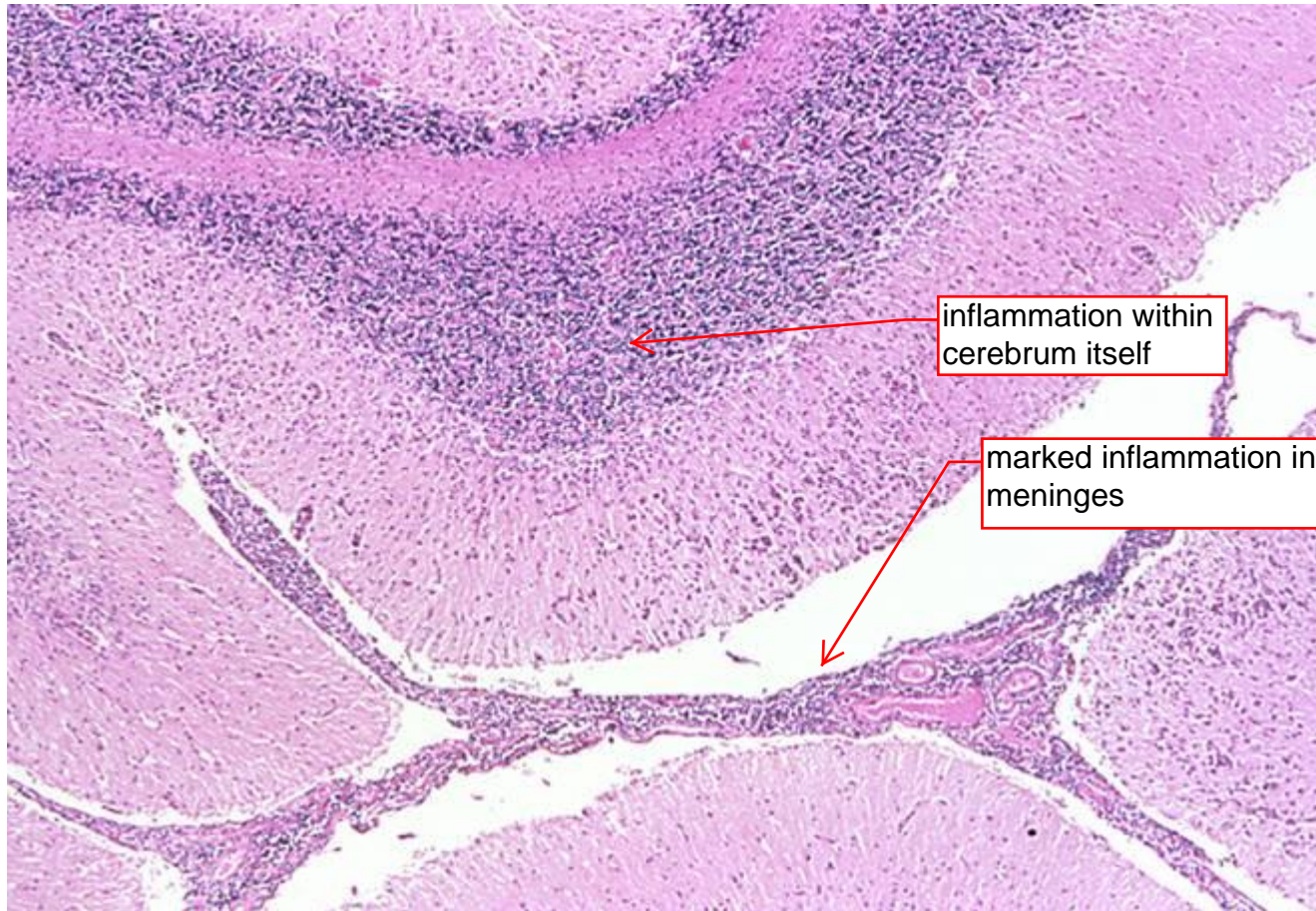
what they're looking for if you had your dog sacrificed to look for rabies...

spasm of laryngeal muscles so cannot swallow so get foaming of mouth

VIRAL ENCEPHALITIS

Rabies

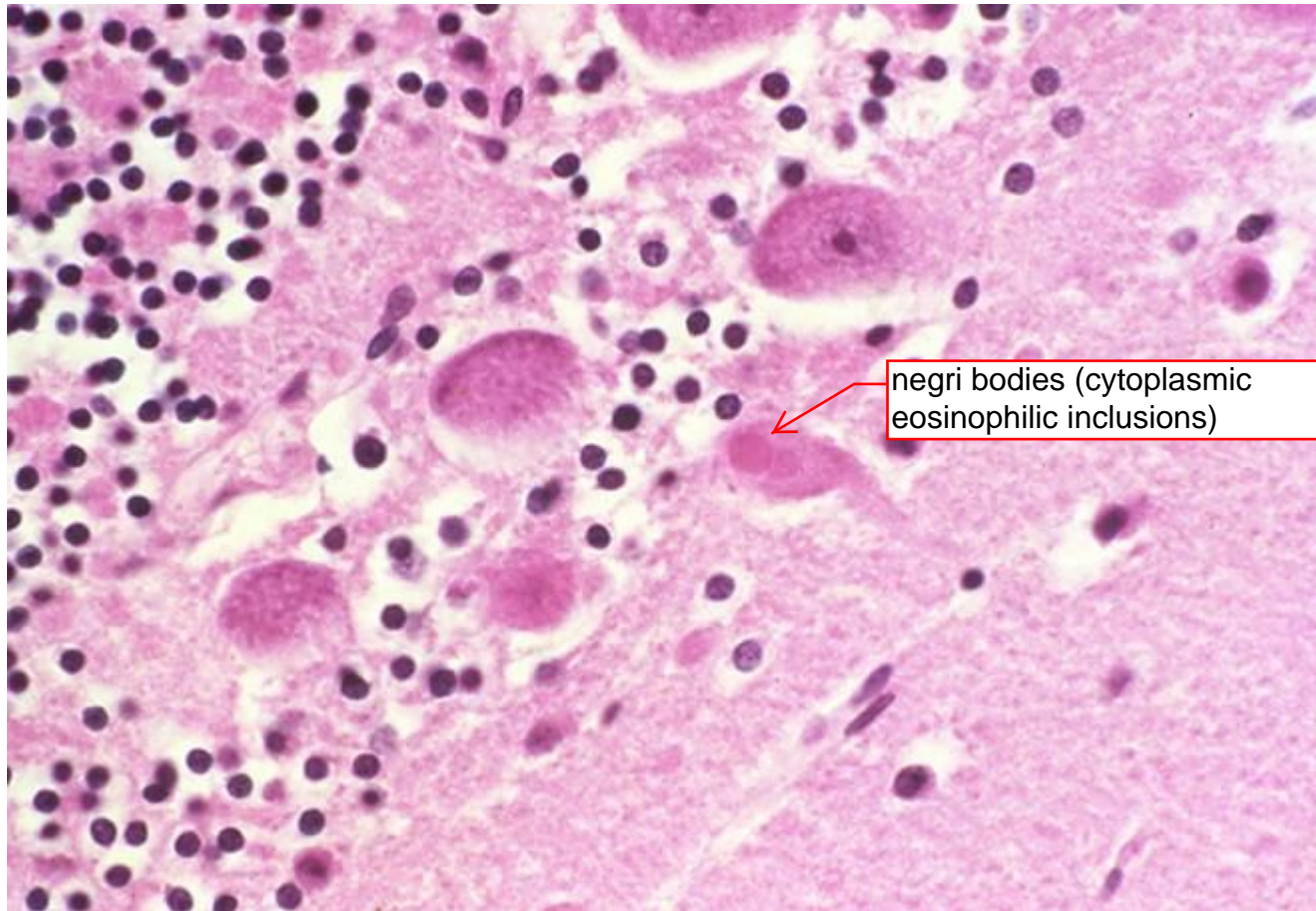
Cerebellum with meningoencephalitis



VIRAL ENCEPHALITIS

Rabies

Negri bodies



PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Creutzfeldt-Jakob disease

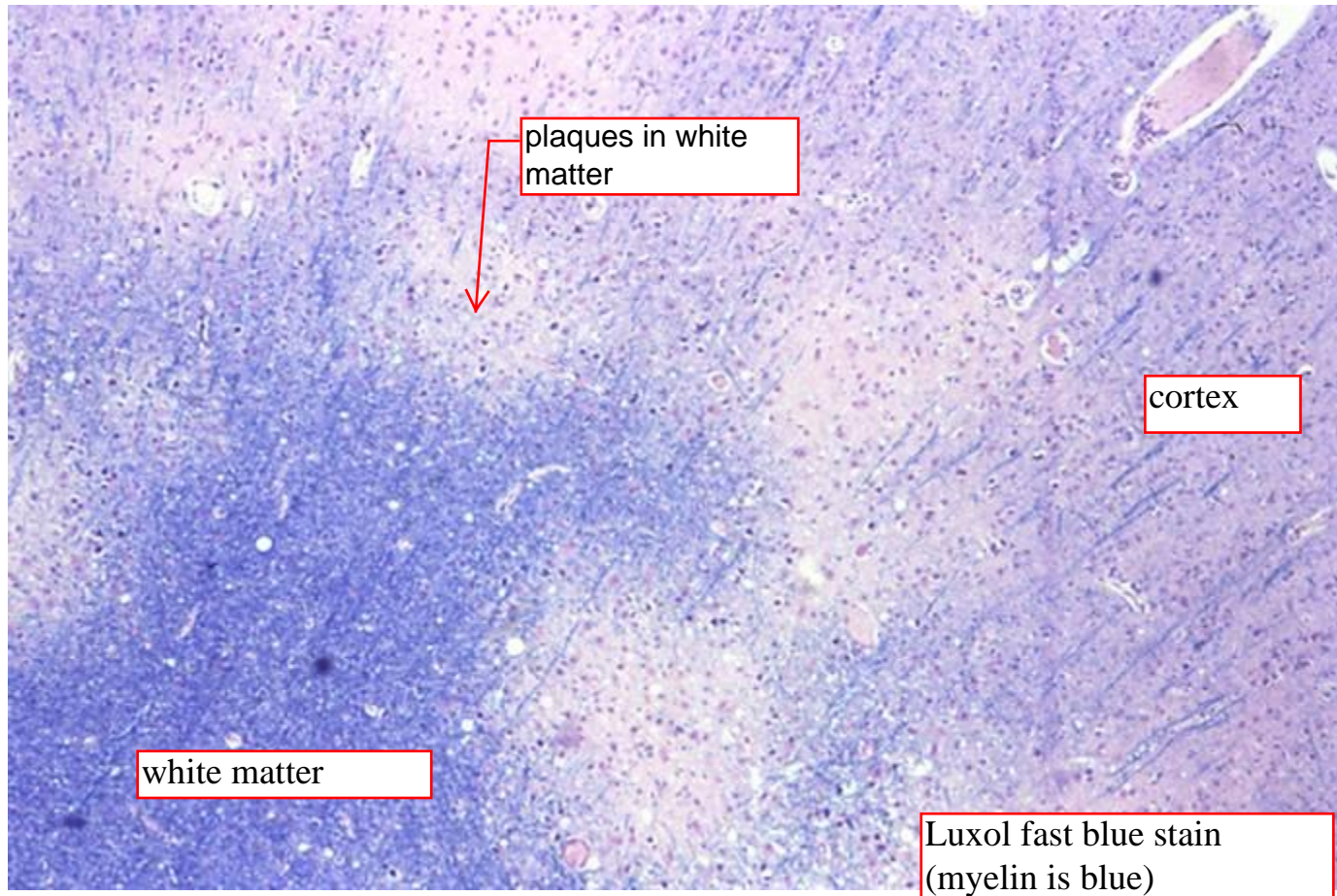


- Polyoma virus (JC virus unrelated to CJD).
- Occurs in immunocompromised hosts.
- Clinical presentation is with dementia, weakness and ataxia.
- Death ensues within 6 months.
- Virus infects oligodendroglia and causes demyelination.

increasing in frequency bc of the HIV/AIDS population,
although it seems to be less common in people on ARV tx

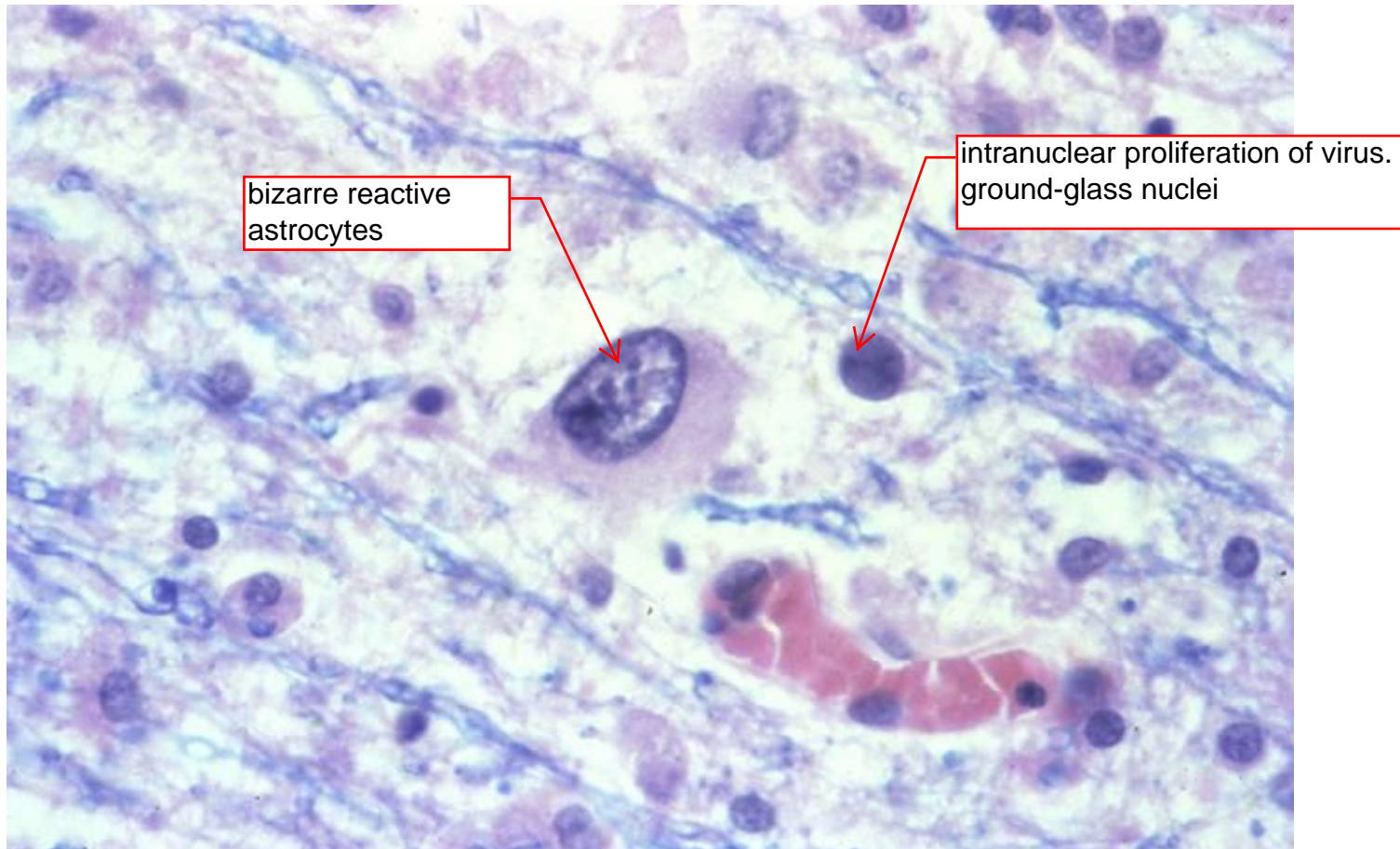
PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Polyoma virus



PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

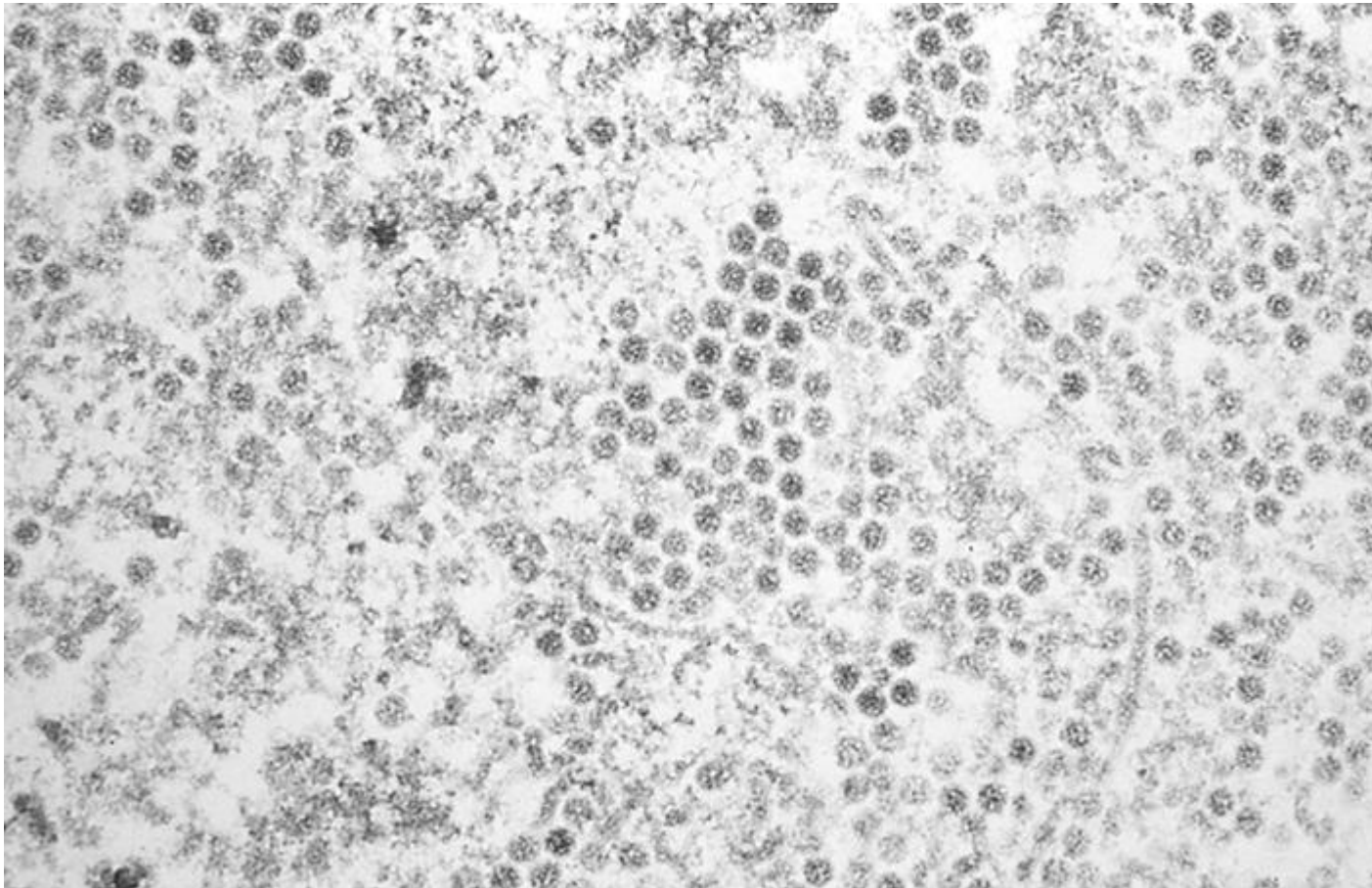
Polyoma virus



PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Polyoma virus

Electromicroscopy
(no elaboration or explanation)



VIRAL ENCEPHALITIS

Measles Virus

Subacute Sclerosing Panencephalitis (SSPE)

very very rare complication of measles virus

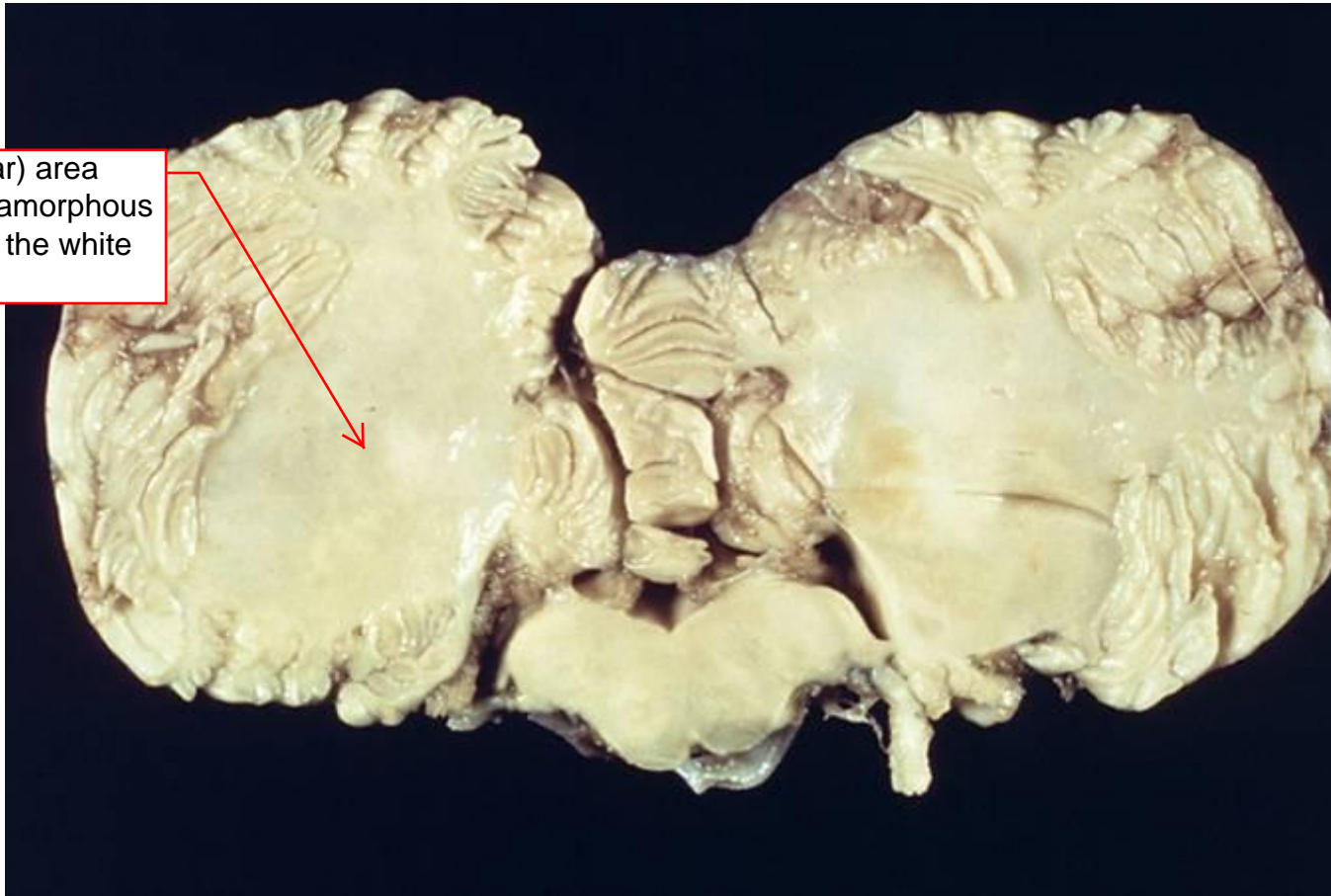
- Persistent measles virus infection.
- The disease has largely disappeared due to vaccination programs.
- However, it is a rare complication in live vaccine recipients.
- Elevated measles virus antibody titer is found in the CSF.

SUBACUTE SCLEROSING PANENCEPHALITIS

Measles

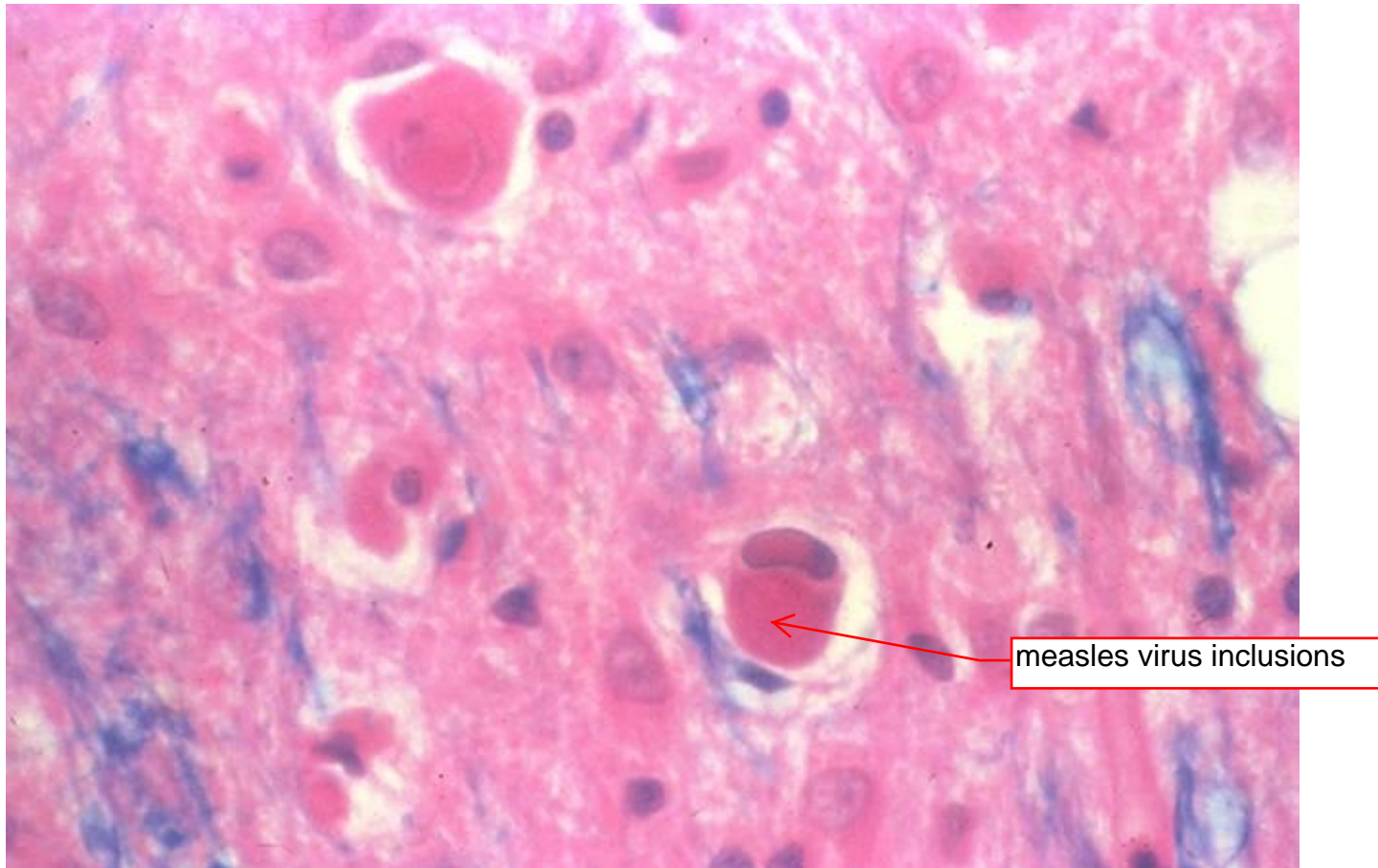
subacute=slowly progressing
sclerosing=scar
panencephalitis=entire brain

sclerosing (scar) area
homogenous, amorphous
appearance to the white
matter



SUBACUTE SCLEROSING PANENCEPHALITIS

Measles

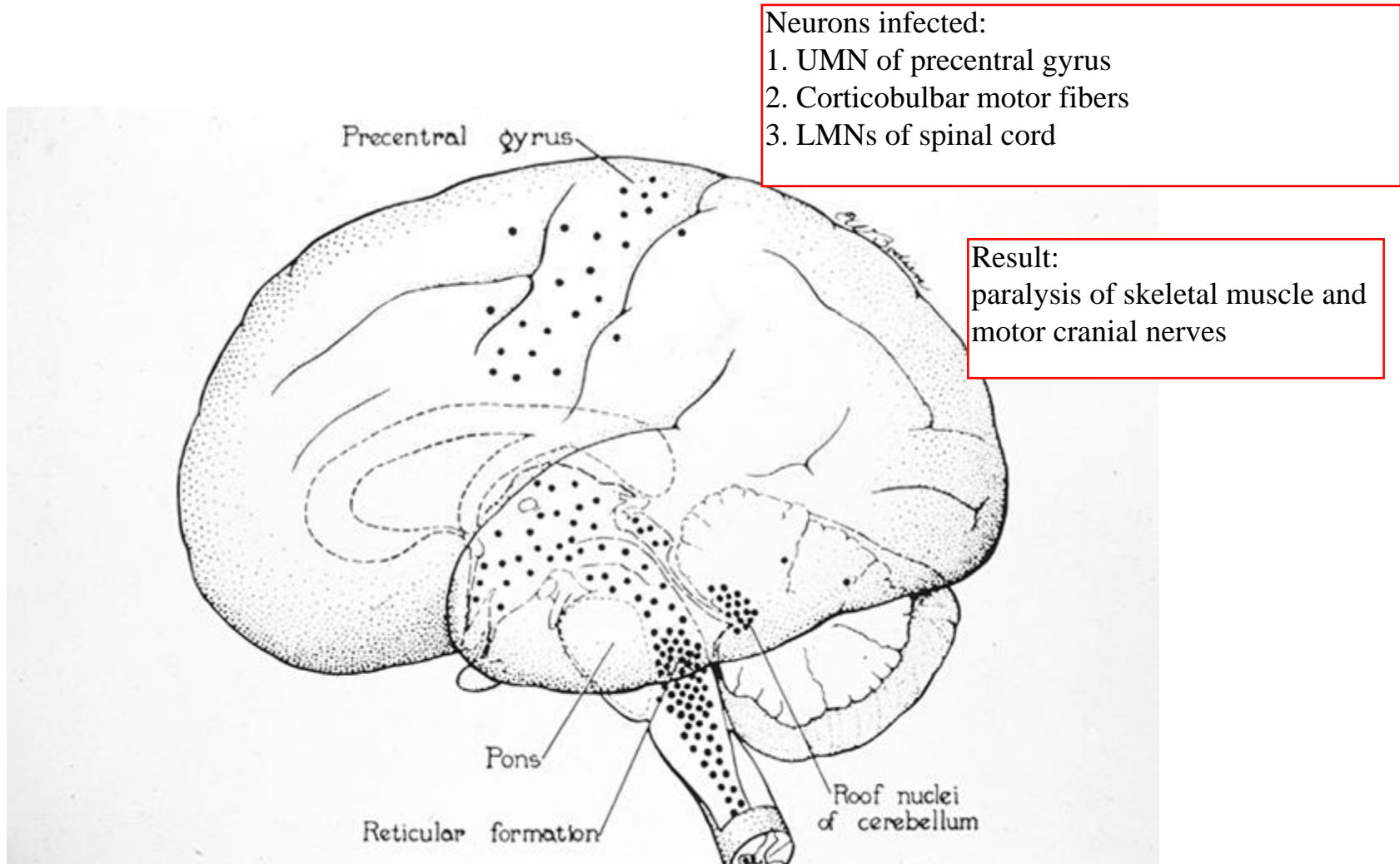


POLIOMYELITIS

Poliovirus

- Disease is caused by a ssRNA virus which is a member of the picorna group of enteroviruses.
- Virus is spread by the fecal-oral route.
 - **Causes a mild gastroenteritis in most people.**
 - **In a few people, it invades the CNS.**
- Viral binding site is present on lower motor neurons. invades LMNs and kills them
- Clinical presentation is with fever, malaise, headache, meningitis and subsequent paralysis.
- Death results from respiratory failure with a mortality of 5-25%.
- Lower motor neurons show chromatolysis and neuronophagia.
- Vaccines have largely eliminated the disease.

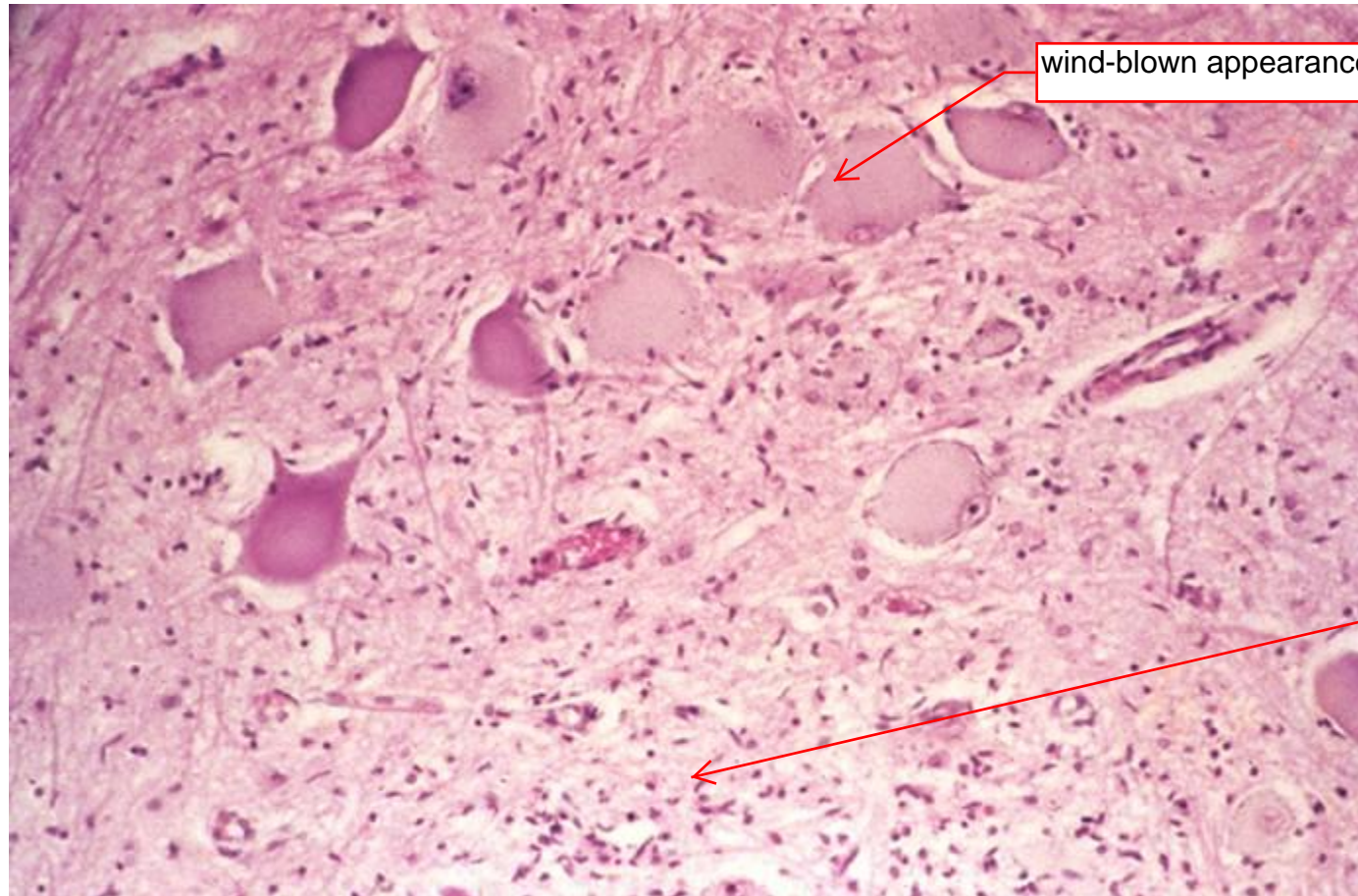
Motor neurons infected by Polio virus



POLIOMYELITIS

Spinal cord anterior horn cells infected by virus

all of these cells are infected by polio



wind-blown appearance of the cells

microglial reaction

Which of the following statements about viral encephalitis is false?

Question about polio: pattern of disease is ascending paralysis, she doesn't know the mechanism/reason behind this pattern

A. It destroys neurons and is always rapidly fatal.

key word

B. Herpes simplex virus preferentially affects the temporal lobes.

C. Polio virus affects the spinal cord.

D. Progressive Multifocal Leucoencephalopathy is uncommon.

E. Symptoms vary with the host and the virus.

HUMAN IMMUNODEFICIENCY VIRUS 1 (HIV-1)

A lot the things she's going to tell us are more applicable to the time before ARV was readily available. These stats aren't really true anymore...

- 60% of AIDS patients develop neurologic dysfunction.
- Neuropathology is seen in 80-90% of AIDS patients.
 - **The neuropathologic changes include direct effects of HIV-1 infection and indirect effects - opportunistic infection and CNS lymphoma.**
- Direct effect of HIV-1 infection
 - **HIV-1 Meningoencephalitis.**
 - **Vacuolar myelopathy.** degeneration of the long tracts in the spinal cord.
no specific histological findings
 - **AIDS-associated myopathy and peripheral neuropathy.** also no specific histological findings

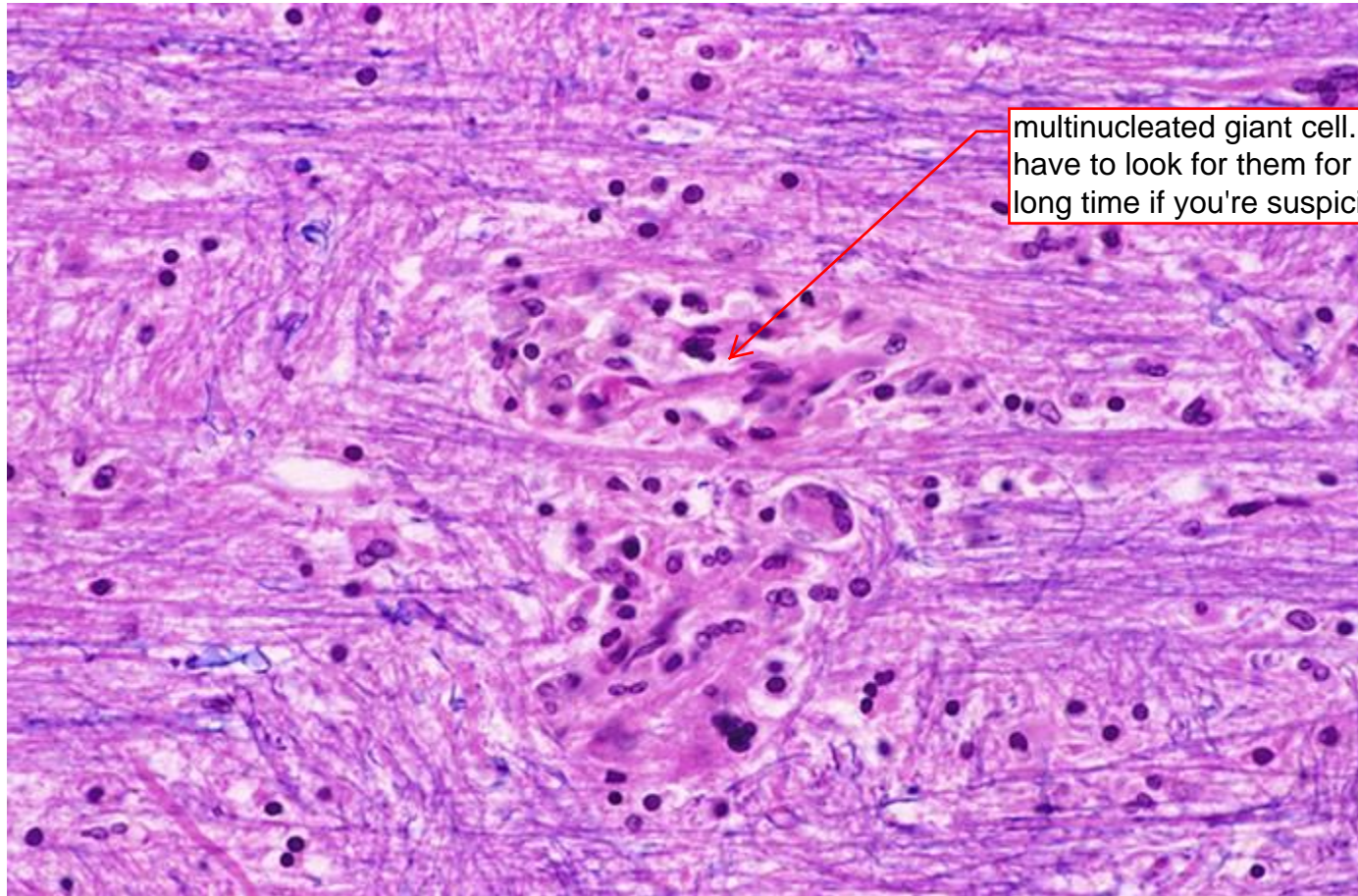
HIV-1

Meningoencephalitis

- Manifest clinically with dementia referred to as “AIDS-related cognitive-motor complex”.
- Neuropathologic findings include:
 - **Multinucleated giant cells** due directly to viral infection
 - **Microglial nodules** due directly to viral infection
 - **Myelin pallor** secondary

HIV-1 Meningoencephalitis

Multinucleated giant cells



multinucleated giant cell.
have to look for them for a long,
long time if you're suspicious

HIV (AIDS)

need to identify and treat

Indirect effects Opportunistic Infections

Bacteria

- Bacterial infections of the CNS in AIDS are uncommon but do occur. AIDS results in T Cells defects.
PMN are ok, they fight of bacteria
- Caustive organisms include:
 - *Mycobacterium avium intracellulare*
 - *Mycobacterium tuberculosis*
 - *Treponema pallidum*
 - rare

HIV (AIDS)

Indirect effects Opportunistic Infections

Viruses

AIDS=no/low T cells, cannot fight off viruses

- Viral infections of the CNS are **very common**
 - **Cytomegalovirus**
 - **Polyoma virus**
 - Causes Progressive multifocal leucoencephalopathy (PML)
 - **Herpes simplex**
 - **Herpes zoster**
 - Causes radiculopathy
 - **Epstein Barr virus**
 - Causes B cell lymphoma

HIV (AIDS)

Indirect effects Opportunistic Infections

Fungi

- Fungal infections of the CNS are **common**
 - *Cryptococcus*
 - **very common**
 - *Aspergillus*
 - **very common**
 - *Coccidioides*
 - **residents of the Southwest**
 - *Histoplasma*
 - **residents of the Mississippi valley**
 - *Zygomycetes*
 - *Candida* sp.

she sees cases mostly due to crypto or aspergillus

HIV (AIDS)

Indirect effects Opportunistic Infections

Parasites

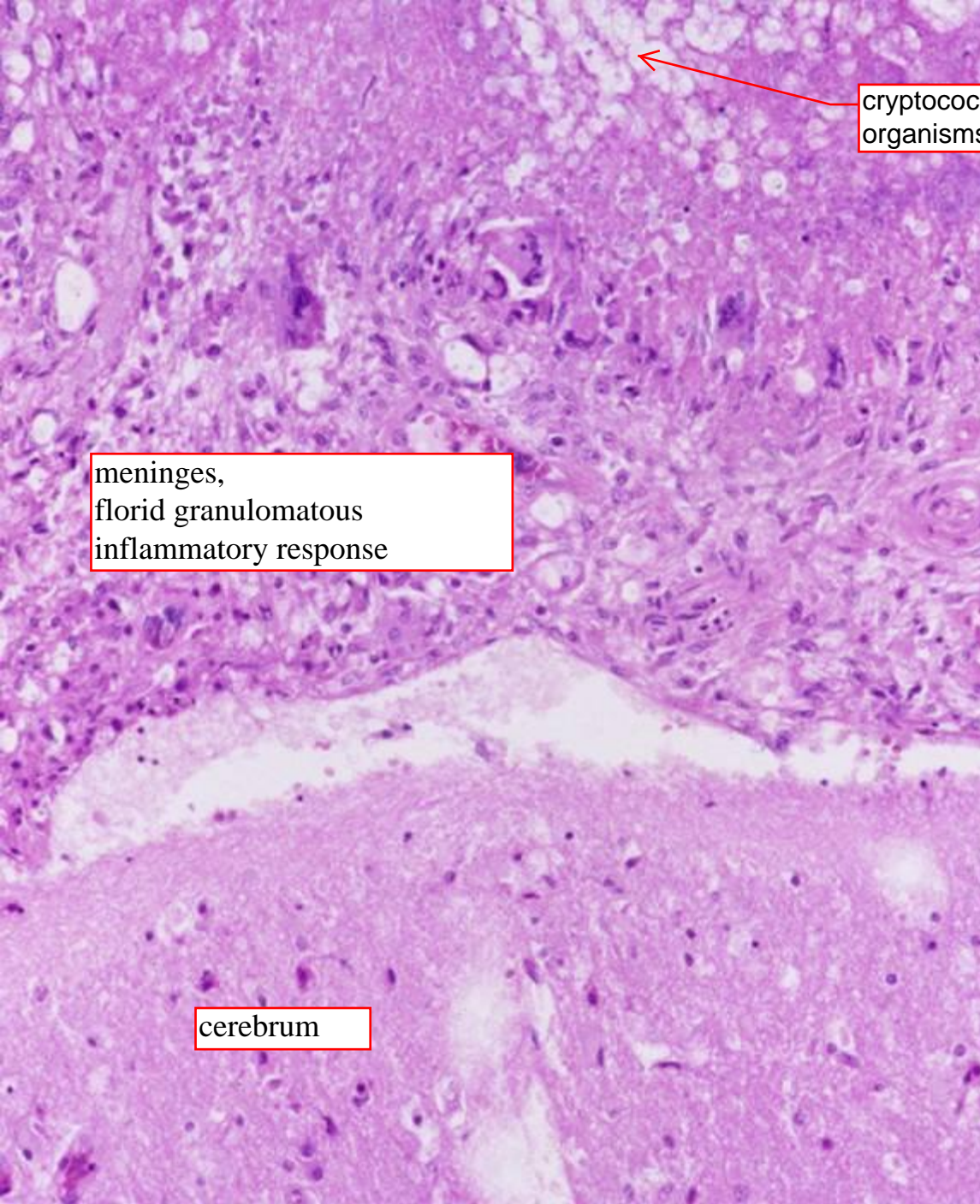
- *Toxoplasma gondii*
 - **Very common**, often treated empirically.
 - **The brain shows necrotizing focal infection with abscesses.**
- *Acanthamoeba*
 - Rare

see abscess on scan of AIDS patient, tx for toxo gondii.
only biopsy if doesn't go away after tx

FUNGAL MENINGOENCEPHALITIS

Cryptococcus neoformans

- Cryptococcus organisms are encapsulated spheres 5 - 15 μ diameter.
- They cause an indolent infection in a immunocompromised host. also common in ppl on chemo for cancer
- There may be minimal tissue reaction.
- India ink examination of the CSF is used for diagnosis



cryptococcus organisms

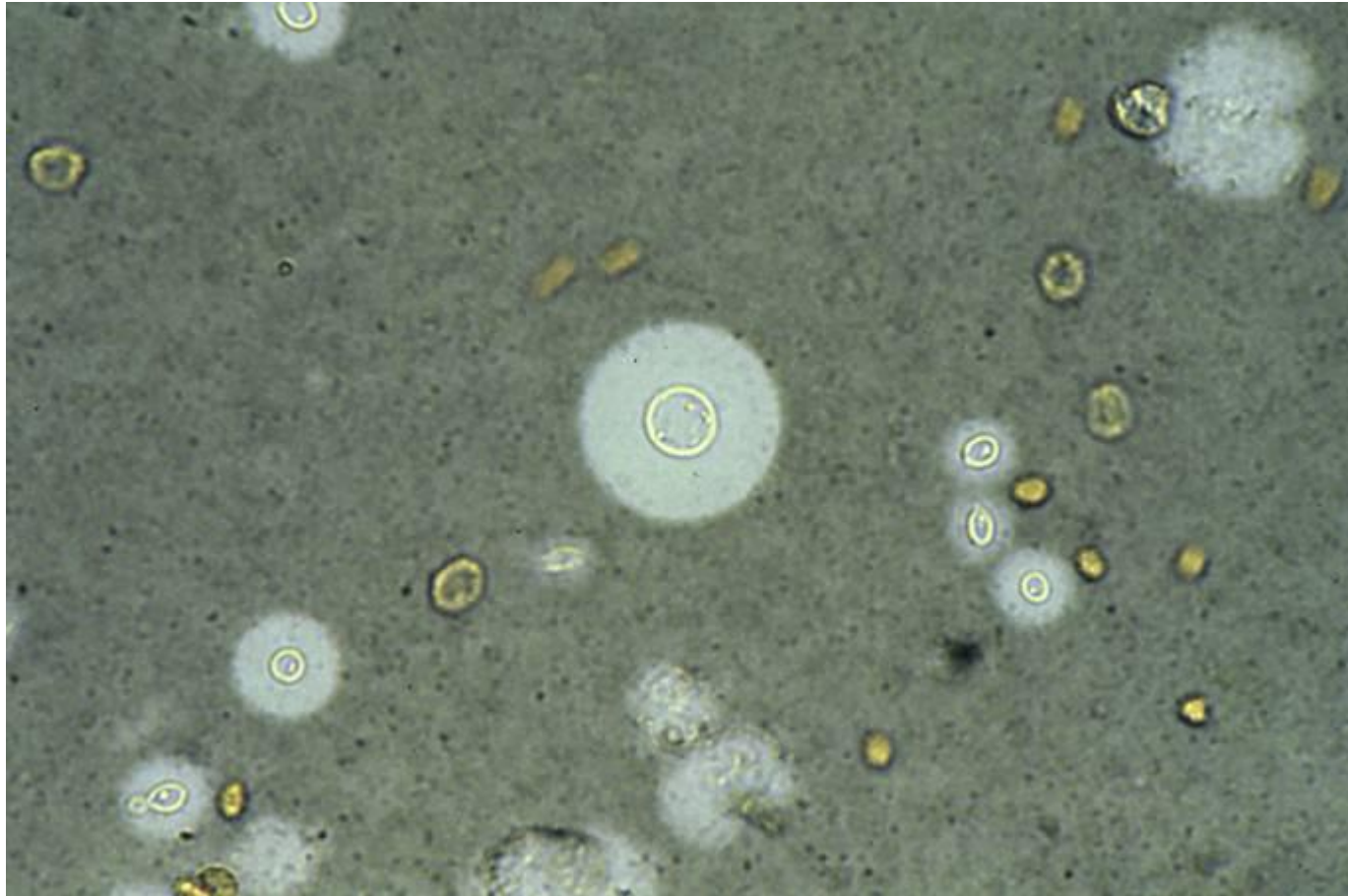
meninges,
florid granulomatous
inflammatory response

cerebrum

Cryptococcus neoformans

Cryptococcus neoformans

INDIA INK



CEREBRAL TOXOPLASMOSIS

- Very common in HIV infected patients
- Symptoms develop over 1-2 weeks and may be focal or diffuse
- CT and MRI show multiple ring enhancing lesion which must be distinguished from CNS lymphoma, TB and fungal infection

gross micrograph of brain
with toxo

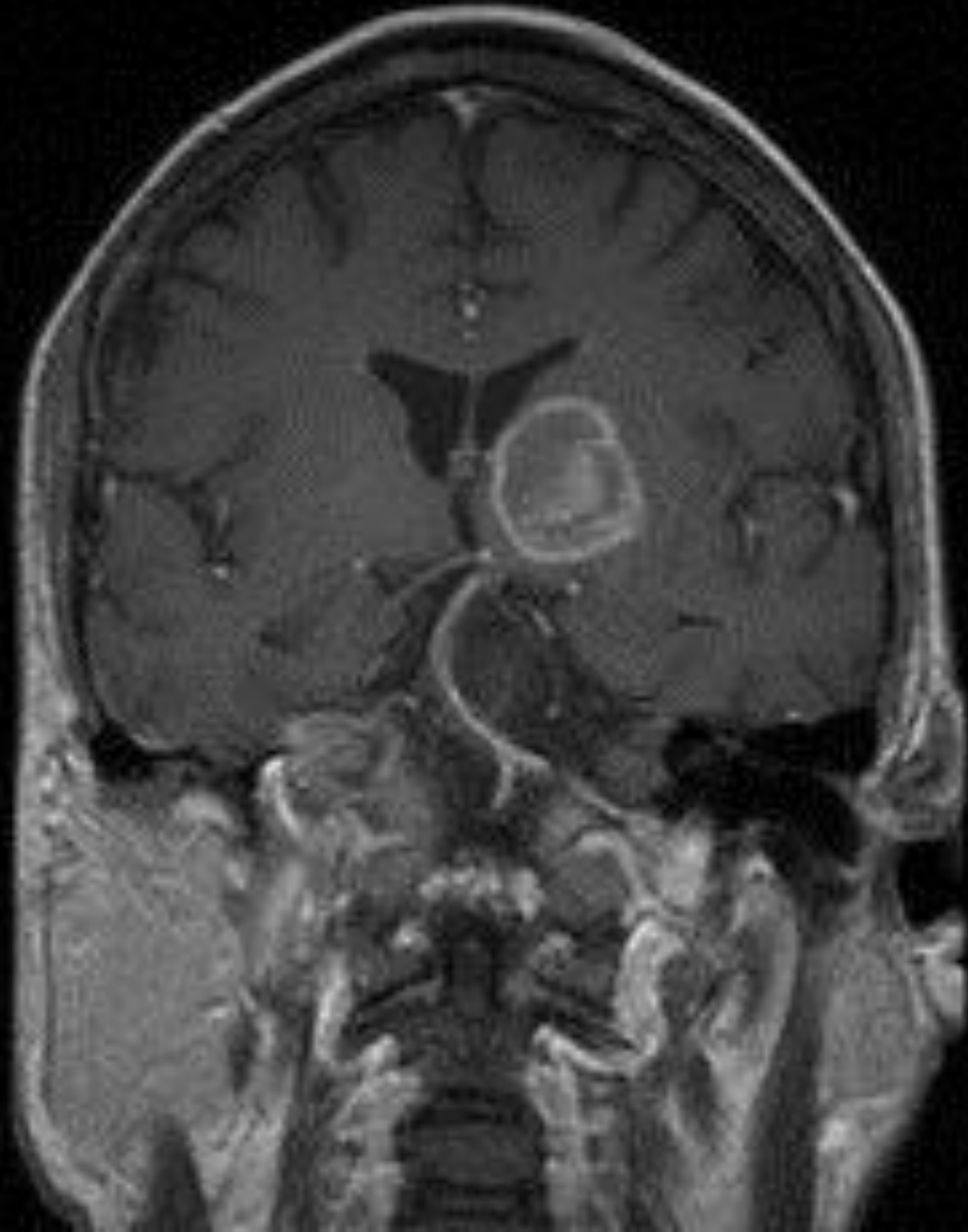


circumscribed abscess in
putamen

in globus pallidus

A

"what it looks like on imaging"



Toxoplasma gondii

Pseudocyst with bradyzoites and free tachyzoites



You see a 40 year old nurse in the ED who has a two week history of fever and sinusitis. EMS was called because she had a grand mal seizure. She had another seizure in the ambulance. After she arrives a CT scan is obtained that shows an **3 cm lesion in the frontal lobe**. What is your diagnosis?

A. Brain abscess

B. Rabies

C. Poliomyelitis

D. Viral encephalitis

E. Syphilis

B-E cause a diffuse process
she has a 3 cm focal process

"this could be a brain tumor, but you don't have that as a choice"

MULTIPLE SCLEROSIS

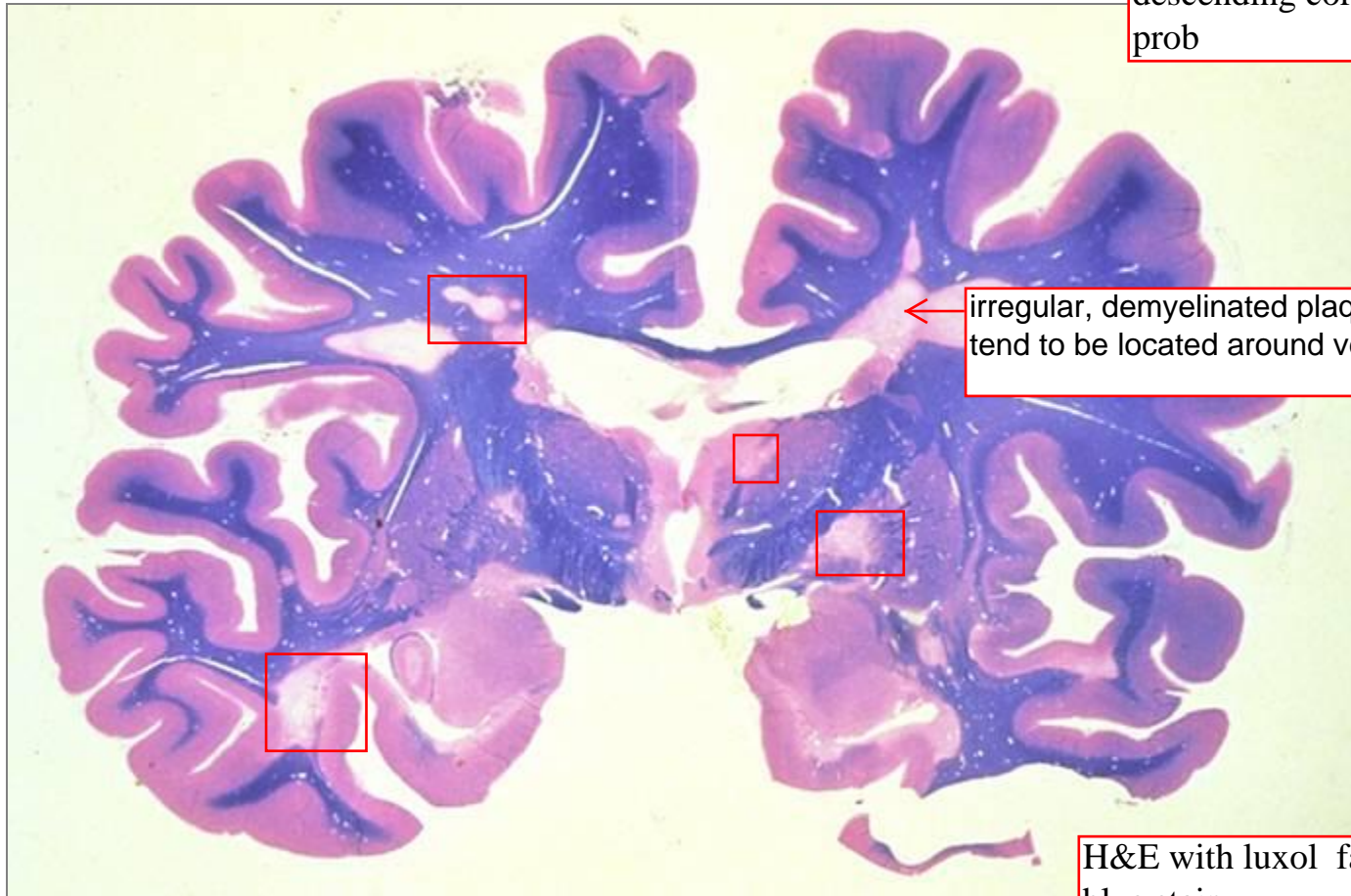
- The onset is acute, at age 20 - 40 years
 - Symptoms are separated in space and time.
 - Clinical course is quite variable with relapses and remissions.
 - Risk factors
 - Living in northern latitudes.
 - Relative affluence.
 - HLA haplotype A2, B7, DW2.
 - Prevalence is 1 per 1000 in US and Europe.
- different parts of the nervous system are involved
- vanishingly rare in Sub-Saharan Africa

MULTIPLE SCLEROSIS

White matter plaques

pattern of plaques is "willy-nilly"

location of plaque determines symptoms
temporal lobe=memory problems
thalamus=motor prob
descending corticospinal tract=motor prob



irregular, demyelinated plaques
tend to be located around ventricles

H&E with luxol fast
blue stain
myelin=blue

MULTIPLE SCLEROSIS PLAQUE

LFB

GLEES



CENTRAL PONTINE MYELINOLYSIS

Clinical features

- Caused by rapid correction of hyponatremia
- Susceptible populations
 - **Alcoholics**
 - **Debilitated patients**

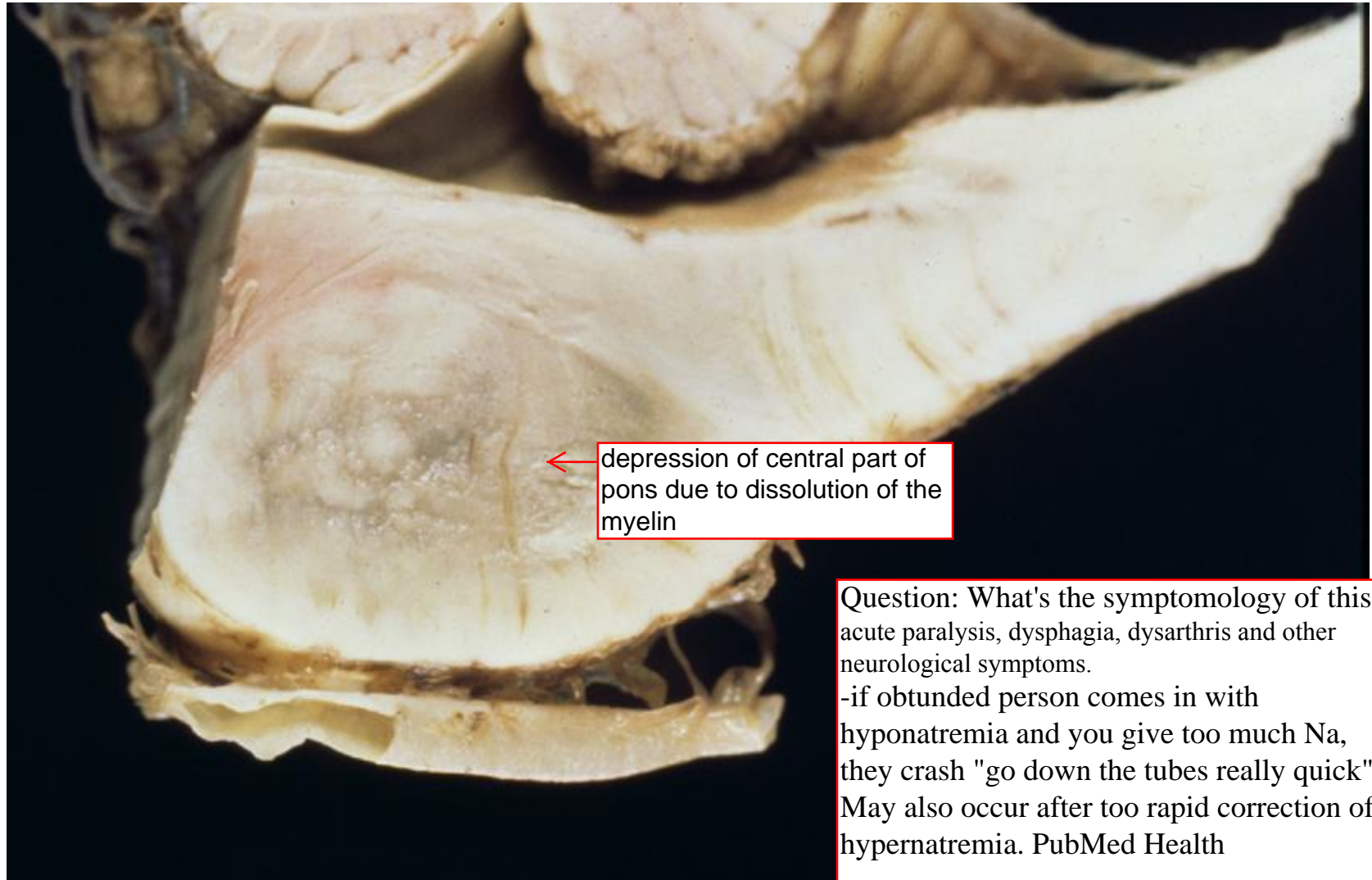
very rare today bc we understand what causes it and therefore how to prevent it

if patient comes in hyponatremic and you put them on normal saline, they could develop this.

-
Avoid by careful fluid management

This could affect anyone who's hyponatremic, these are just populations that are often hyponatremic!

CENTRAL PONTINE MYELINOLYSIS



← depression of central part of pons due to dissolution of the myelin

Question: What's the symptomology of this? acute paralysis, dysphagia, dysarthria and other neurological symptoms.

-if obtunded person comes in with hyponatremia and you give too much Na, they crash "go down the tubes really quick". May also occur after too rapid correction of hypernatremia. PubMed Health

A summary

Question: Are the symptoms of JC virus similar to MS except that it doesn't get better/relieved?

-

Yes! Also, JC virus only in immunocompromised
MS in otherwise healthy people

Bacterial Infections

Meningitis

Cerebritis

Abscess

1. Meningitis: inflammation of arachnoid and pia
2. Cerebritis: inflammation of the brain itself
3. Abscess: A localized process

Viral Infections

Meningitis

Meningoencephalitis

Meningoencephalitis: inflammation of meninges and the brain itself

HSV, CMV, Polio, JCV, SSPE

HIV

Opportunistic infections

Multiple Sclerosis

Central Pontine Myelinolysis

HAVE A GOOD DAY!