



Learning Objective- contd. from CNS-1

16. Describe the gross and microscopic morphologic features of bacterial meningitis



GENERAL FEATURES OF TISSUE DAMAGE IN THE CNS CAUSED BY INFECTIOUS AGENTS



- ***Direct injury*** to neurons or glia by the infectious agent
 - Viral cytopathic effects (will be discussed in part 3)
- ***Indirect injury***
 - Through the elaboration of **microbial toxins**
 - Through the destructive effects of the **inflammatory response** (e.g. PMNs in acute bacterial meningitis)
 - As a result of **vascular damage** (e.g. endothelial damage leading to hemorrhage or thrombosis and infarct)
 - As a result of **increased intracranial pressure** due to edema or hemorrhage
 - As a result of **immune-mediated mechanisms**
- ***Changes resulting from repair***
 - **Gliosis** (can lead to seizures)
 - **Hydrocephalus** due to fibrotic occlusion of the foramina or the cerebral aqueduct

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GROSS MORPHOLOGY OF BACTERIAL MENINGITIS

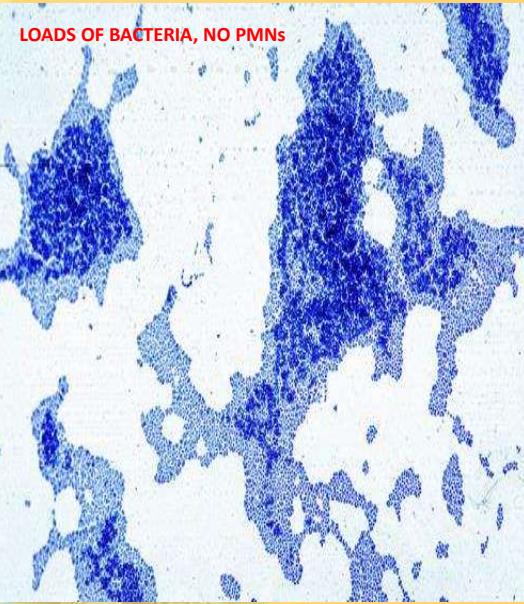


- Purulent exudate covers the meninges and tracks along the blood vessels
- Location varies depending on the type of the organism:
 - *H. influenza*
Basal
 - *Neisseria meningitidis* and *Streptococcus pneumoniae*:
On the convexity of the brain
- Inflammation may extend to the ventricles
- The tough glia limitans forms a barrier on the surface of the cortex and usually prevents spread of infection into the sub-pial gray matter



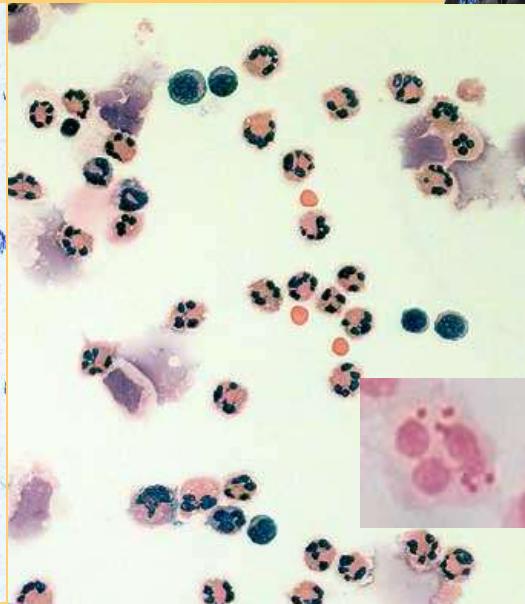
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CSF IN "SUPER ACUTE" FULMINANT BACTERIAL MENINGITIS



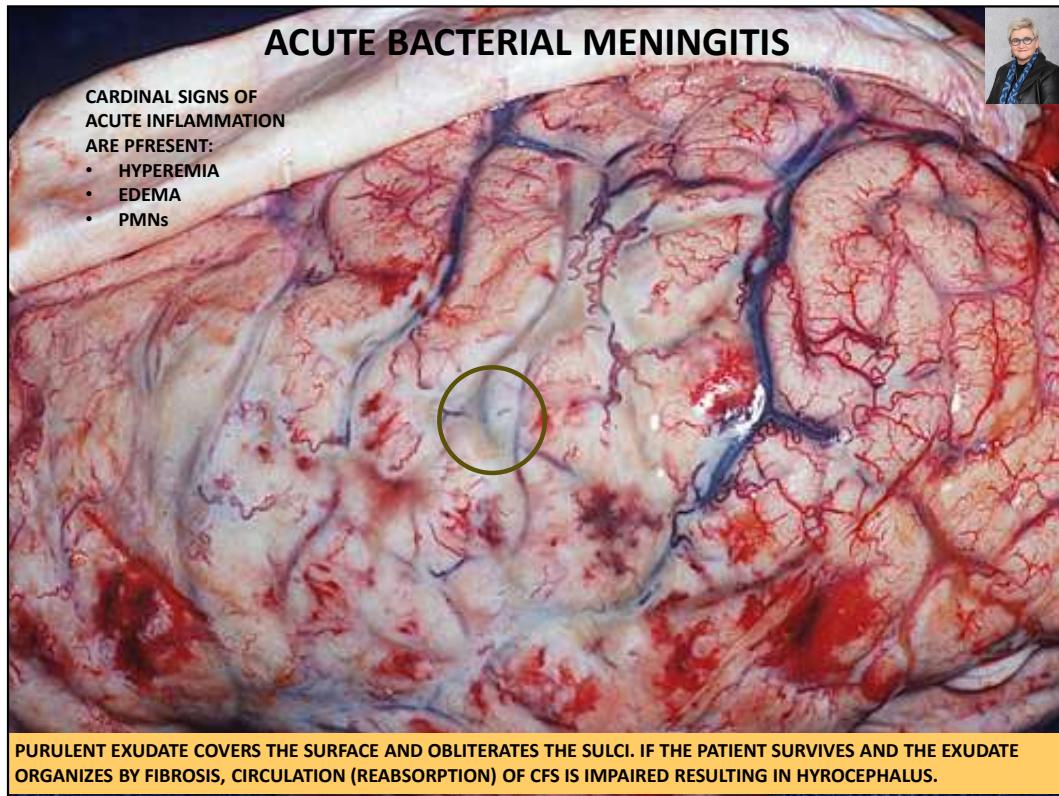
LOADS OF BACTERIA, NO PMNs

TYPICAL CSF IN ACUTE BACTERIAL MENINGITIS



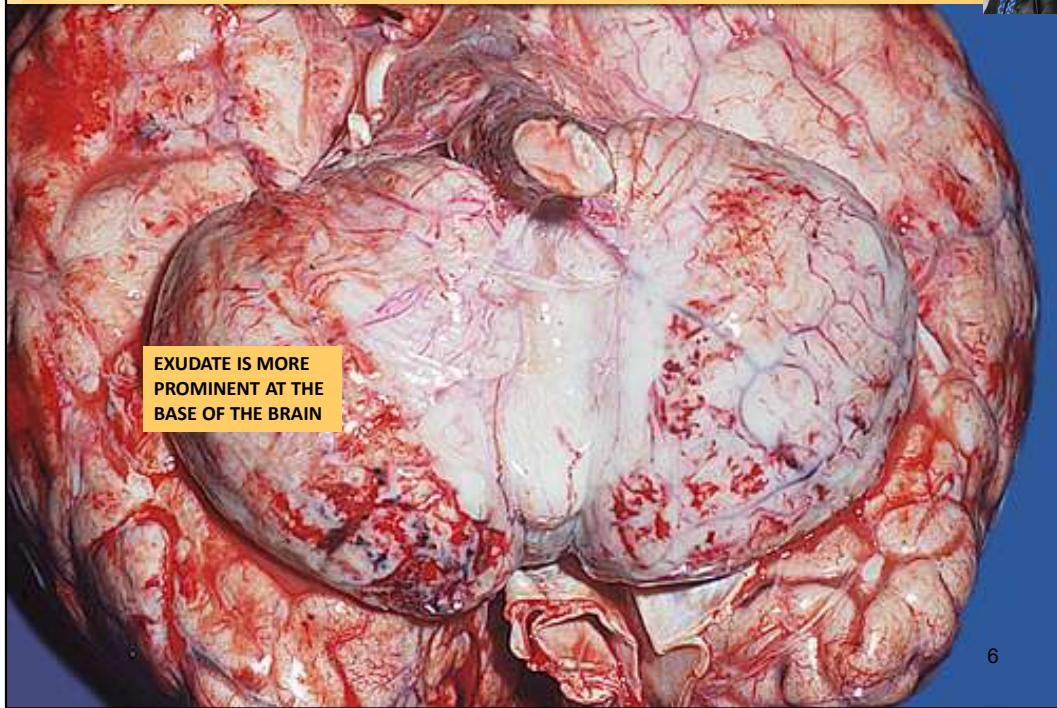
Note the absence of PMNs in early meningitis. Bacteria can multiply freely in the CNS before there is any inflammatory reaction (normal CSF has no PMNs).

Note numerous PMNs, occasional lymphocytes and many disintegrating cells. Gram stain shows gram-negative intracellular diplococci in *Neisseria* meningitis .



This was a case of pneumococcal meningitis. Meningococcal meningitis would look the same.

H. INFLUENZA MENINGITIS





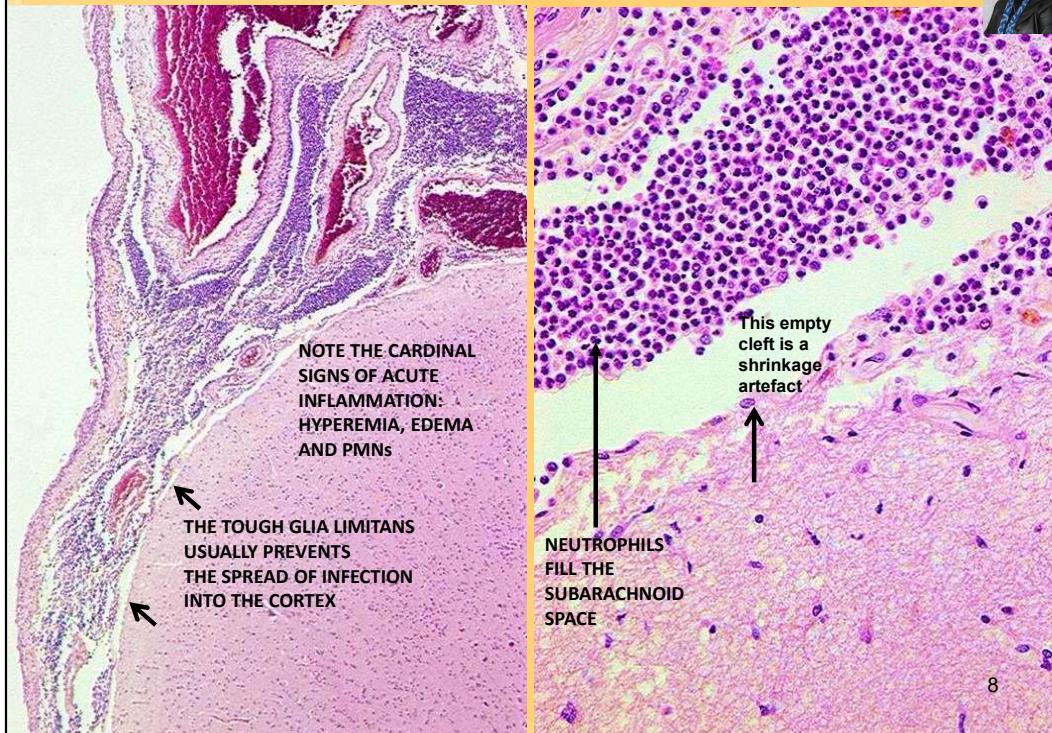
MICROSCOPIC FINDINGS IN ACUTE BACTERIAL MENINGITIS

- PMNs fill the subarachnoid space
- Inflammatory cells are predominantly around leptomeningeal blood vessels
- Microorganisms can be found especially in untreated cases
- Vascular injury by bacterial toxins may cause venous thrombosis
- Hemorrhagic infarction results from vascular occlusion



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ACUTE BACTERIAL (=SUPPURATIVE) MENINGITIS



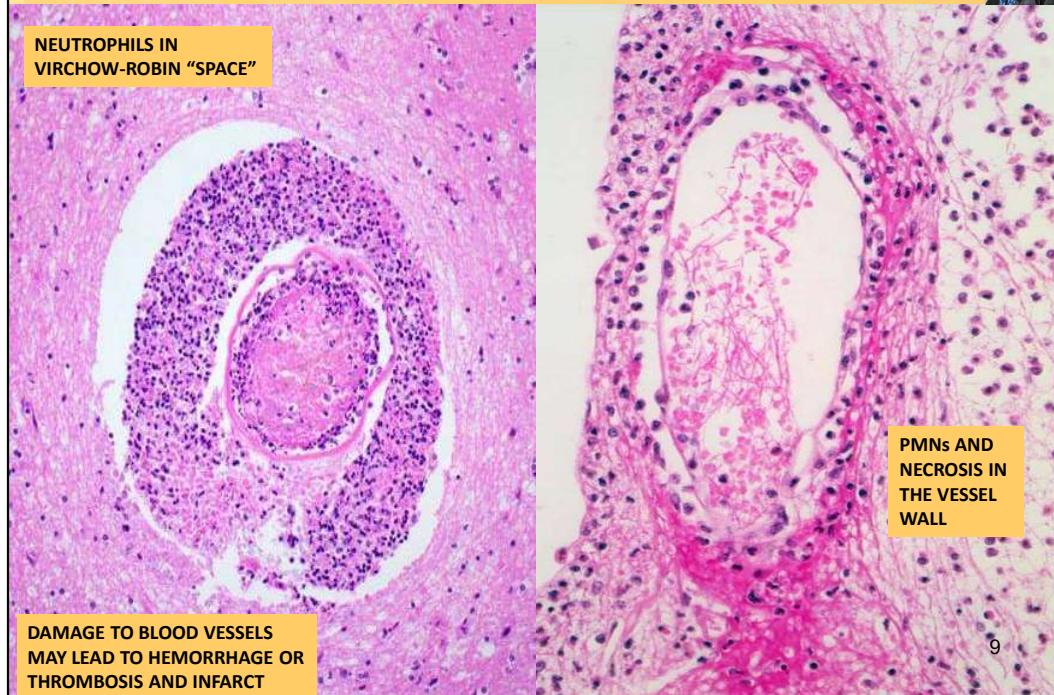
78 y o woman. Cerebrum and meninges. **Diagnosis:** Bacterial meningitis.

Description: The subarachnoid space is filled with pus. **Clinical findings:**

Diabetes mellitus. **Stain:** HE. Neutrophilic exudate involves the meninges that have prominent dilated vessels. There is edema and focal inflammation extending down via the Virchow-Robin space) into the cortex to the right. This acute meningitis is typical for bacterial infection.

This edema can lead to herniation and death. Resolution of infection may be followed by adhesive arachnoiditis with obliteration of subarachnoid space leading to obstructive hydrocephalus.

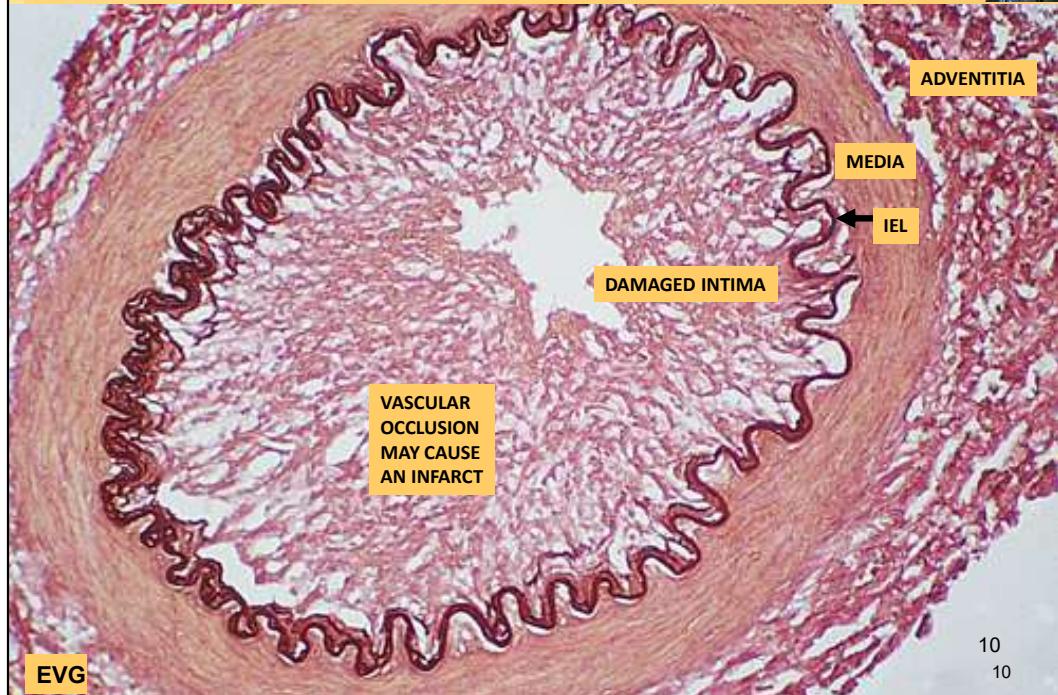
VESSELS IN ACUTE BACTERIAL MENINGITIS



66 y o woman. Cerebrum. **Diagnosis:** Acute suppurative meningitis.

Description: Neutrophils in the subarachnoid space and within the Virchow-Robin space (left). Leptomeningeal vessel with necrosis of the vessel wall (right).

COMPLICATION OF BACTERIAL CNS INFECTION: INTIMAL DAMAGE IN AN ARTERY CAUSED BY BACTERIAL TOXINS

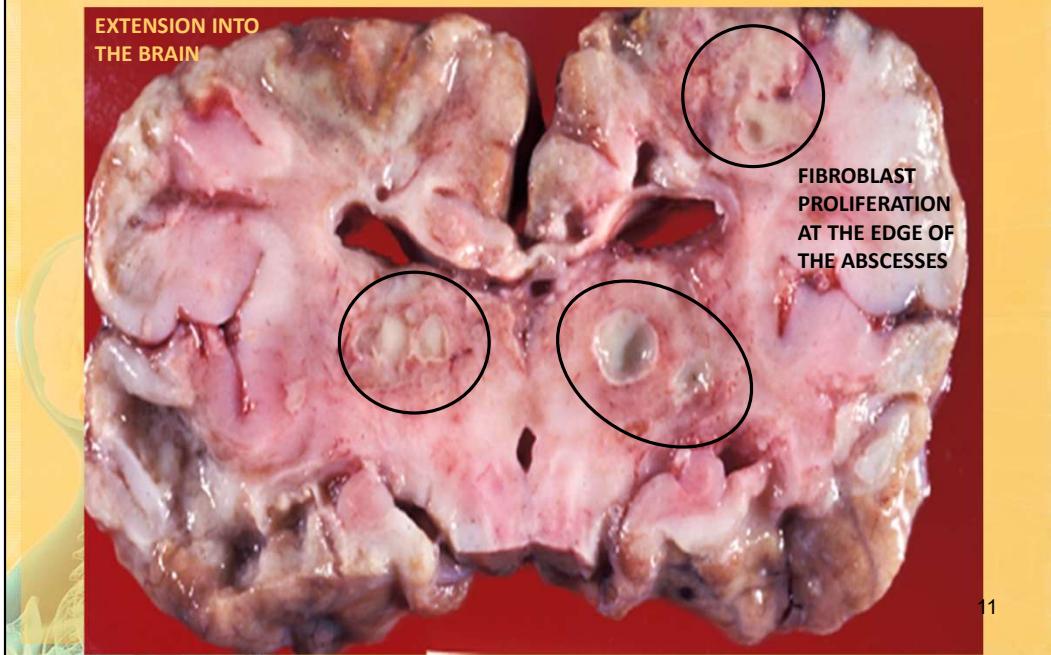


EVG =Elastic van Gieson stain.

IEL = Internal elastic lamina

NEONATAL GROUP B STREPTOCOCCAL MENINGITIS

COMPLICATION: EXTENSION INTO THE BRAIN (ENCEPHALITIS) AND
MULTIPLE ABSCESSSES



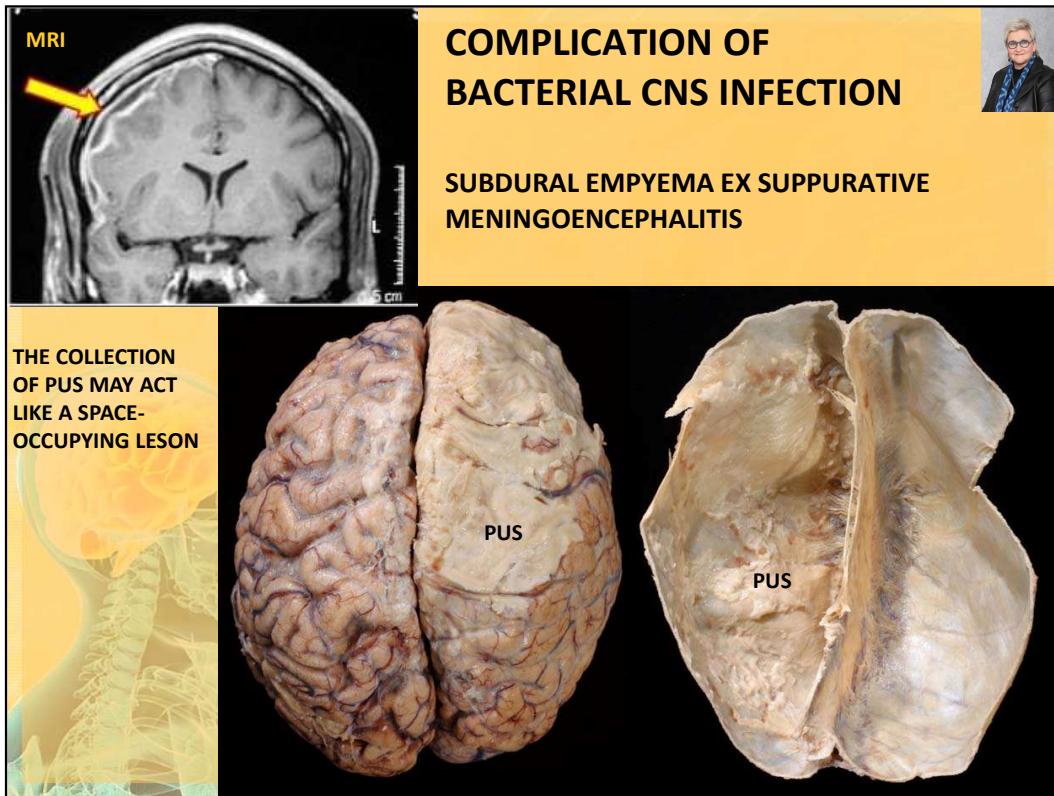
NEONATAL BACTERIAL MENINGITIS

COMPLICATION: SEVERE BRAIN ATROPHY



FLUID-FILLED BAG-LIKE CEREBRUM AND RELATIVELY SPARED CEREBELLUM

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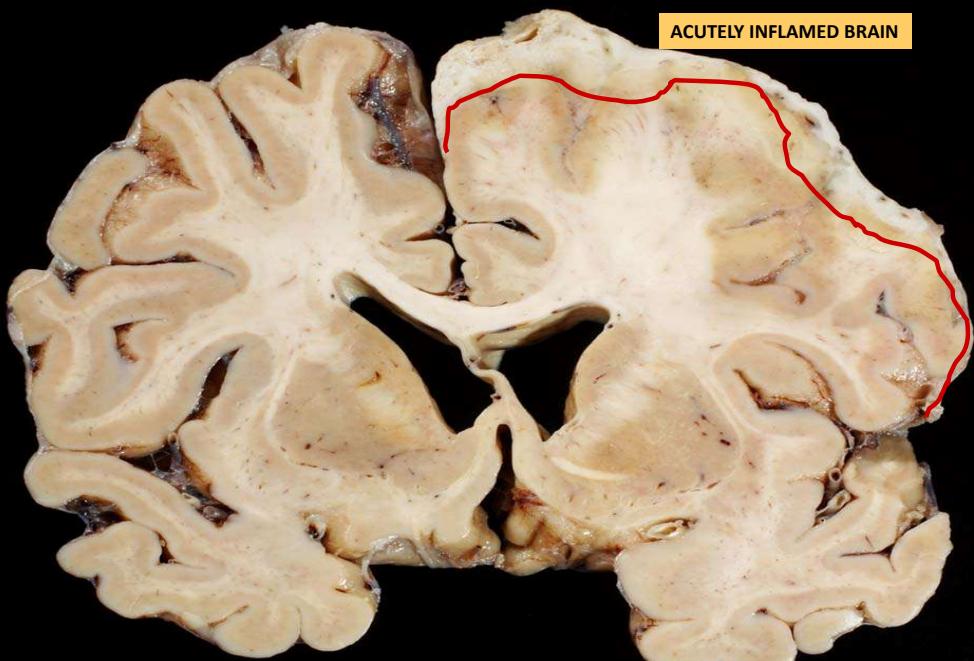


74 y o man. Diagnosis: Suppurative meningoencephalitis (pneumococci), subdural empyema. **Description:** The right hemisphere and the subdural space are covered by pus (subdural empyema). **Clinical findings:** Chronic alcoholic with diabetes mellitus. The patient was somnolent and febrile on admission to the hospital and was found to have pneumococcal sepsis and endocarditis. He had right frontotemporal ischemia with left hemiparesis. He suffered rhabdomyolysis, went into acute renal failure and required tracheostomy for ventilatory support.

SUPPURATIVE MENINGOENCEPHALITIS



ACUTELY INFLAMED BRAIN



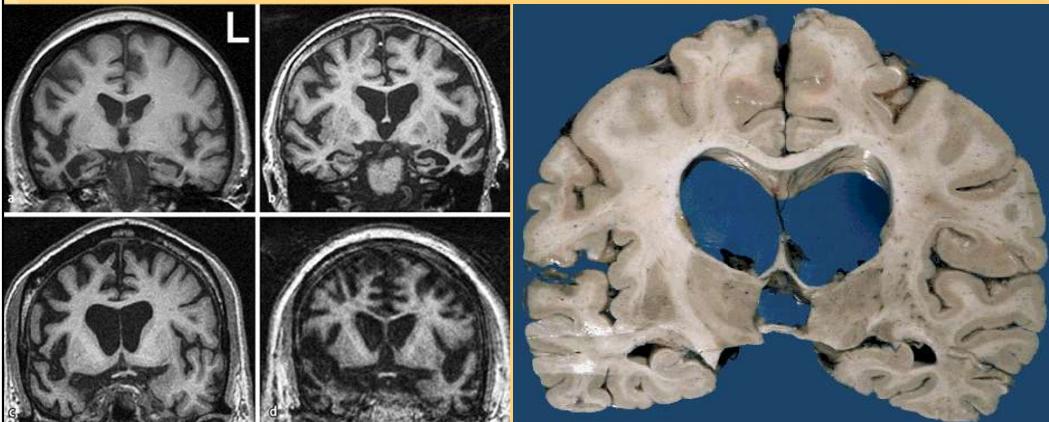
SUBDURAL EMPYEMA WITH EXTENSION OF THE INFLAMMATORY PROCESS INTO THE BRAIN.

74 y o man. Diagnosis: Suppurative meningoencephalitis (pneumococci), subdural empyema.

COMPLICATION OF MENINGITIS: HYDROCEPHALUS



- Meningeal fibrosis and/or obstruction of foramina and/or cerebral aqueduct can lead to hydrocephalus.



- Communicating hydrocephalus:
 - Flow within the liquor space is unobstructed: foramina are patent, but absorption of the CSF is impaired because of meningeal fibrosis.
- Non-communicating hydrocephalus:
 - Foramina and/or cerebral aqueduct are obstructed.

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Left: Exit of CSF from the fourth ventricle became obstructed by fibrosis and hydrocephalus ensued.

MRI Coronal sections T1WI (T1weighted images) demonstrate varying degree of atrophy in 4 different patients. Note that the atrophy is diffuse and includes both enlargement of the ventricles and widening of the sulci.

Right: 19 yom. Diagnosis: Hydrocephalus s/p purulent meningitis.

Description: The ventricles are dilated and the cerebral aqueduct is occluded by fibrosis. **Clinical findings:** Meningococcal meningitis 9 months ago.

Cranial nerve deficits and non-communicating hydrocephalus resulted from organization of fibrinopurulent exudate.

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM PART 2

Localized infections Abscesses/ Cysts etc.

- Integrated Team Teaching
- Bringing Clinical Aspects and Basic Science together in one lecture



Chitra Pai,
MD, D(ABMM)



Elaine Ho,
DO



Evan Hermel,
PhD

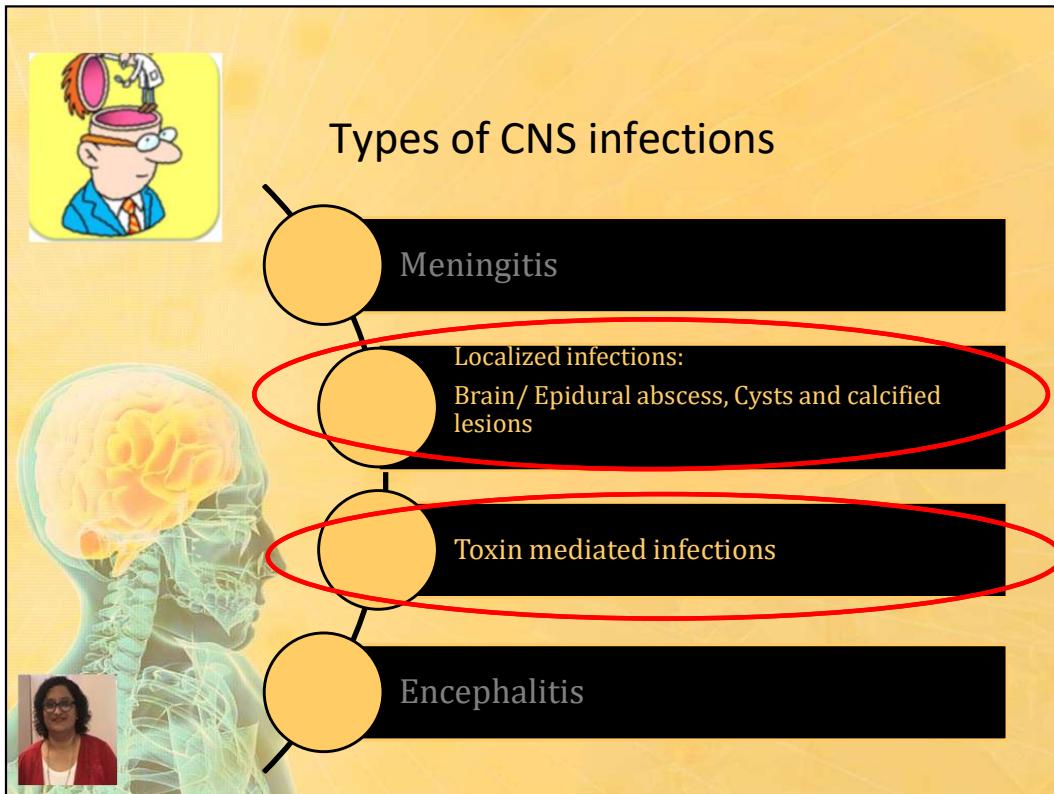


Liisa A. Russell,
MD

Learning Objectives for CNS-2

- 1) Enumerate localized lesions of the CNS. Describe the CNS abscesses including different intracranial and spinal abscesses.
- 2) Associate the various underlying conditions with abscesses.
- 3) Describe the clinical presentations and complications.
- 4) Enumerate etiologic agents causing abscesses, cystic lesions and calcified lesions.
- 5) Describe the underlying pathology involved in these lesions.
- 6) Describe the imaging modalities used in CNS infections. Describe ring enhancement and its appearance in imaging.
- 7) Discuss the appropriate work-up and treatment of abscesses
- 8) Describe the morphology, characteristics, epidemiology and pathogenesis of parasites causing cystic and calcified lesions.
- 9) Describe the laboratory diagnosis and treatment of these infections.
- 10) Describe the gross and microscopic morphologic features of these infections





- 1) Enumerate localized lesions of the CNS.

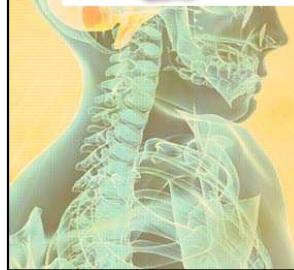
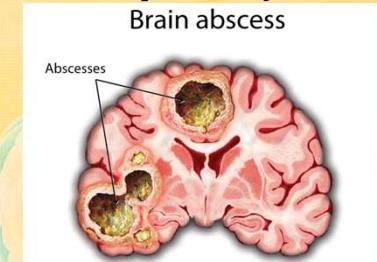
Many of the localized lesions present as intracranial space occupying lesions



CNS ABSCESS-Brain abscess

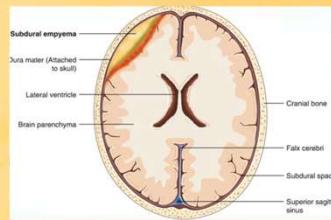
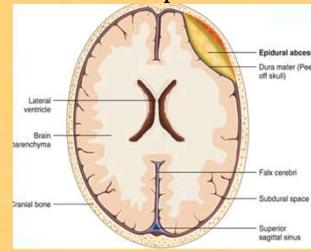
Intracranial abscess

- Focal collection of pus in brain parenchyma



Intracranial epidural abscess

- Collection of purulent material between the dura and the bones of the skull or spine



Subdural Empyema

- Collection of purulent material below the intact dura within the skull

Enumerate localized lesions of the CNS. Describe the CNS abscesses including different intracranial and spinal abscesses.

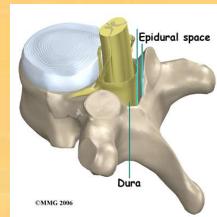
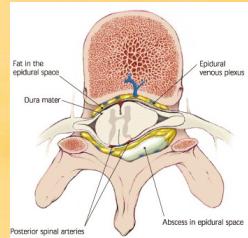


CNS ABSCESS-Spinal epidural abscess

- Collection of purulent material between the dura and the bones of the skull or spine

EPIDURAL ABSCESES Spinal > intracranial (9:1)

Intracranially, the dura is adherent to bone. Loose association between the dura and vertebral bodies enables extension of spinal epidural abscess to numerous levels

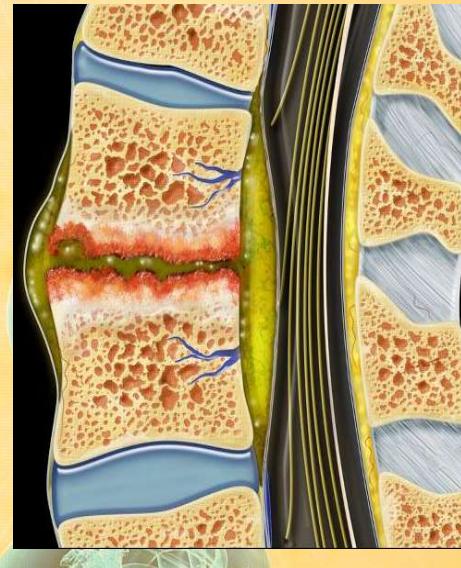


Loose association between the dura and vertebral bodies enables extension of spinal epidural abscess to numerous levels - frequently resulting in extensive neurological findings and often necessitating multiple laminectomies.

The degree of neurologic recovery after surgery correlates with the duration and initial severity of the neurologic defect



Epidural abscess due to discitis



MRI showing discitis with abscess extending [21](#) to the epidural space

MRI of 62 yo female with discitis with abscess extending to the epidural space. The bright area in the vertebrae above and below the area are due to osteomyelitis involved with the discitis.



PATHOGENESIS

Route of entry

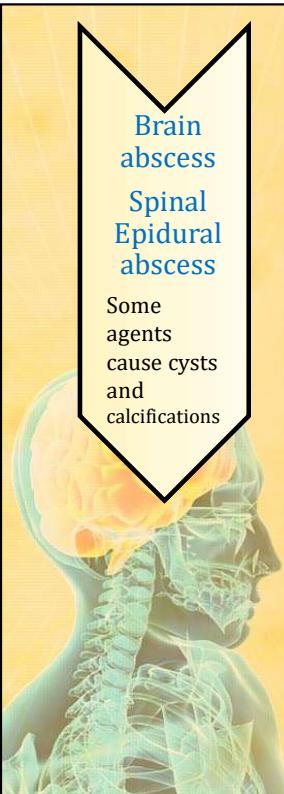
- a) Direct spread from contiguous foci (40-50%). Eg. from sinusitis/mastoiditis/dental infection
- b) Hematogenous (25-35%)-following sepsis/ Infective endocarditis
- c) Penetrating trauma/surgery (10%)-Fracture of skull/ neurosurgery
- d) Cryptogenic (15-20%)-unknown cause

Manifestations

- ✓ Headache
- ✓ Fever
- ✓ Altered mental status
- ✓ Severe back ache(spinal)
- ✓ Paralysis
- ✓ Focal neurologic findings
- ✓ Loss of bladder/ bowel control
- ✓ Others-Nausea/vomiting, Seizures, Nuchal rigidity, Papilledema

Complications

- Death. **Mortality rate** of 2%-20%
- Permanent neurologic sequelae.



Etiologic agents



Bacteria:

- *Staphylococcus aureus*
- *Aerobic and anaerobic streptococci*
- *Enterococcus*
- *Pseudomonas*
- *Non sporing anaerobes*
- *Mycobacterium tuberculosis*
- *Nocardia*

Fungi:

Mucor/ Rhizopus

Cryptococcus neoformans (also cause cysts and calcifications)

Parasite:

Toxoplasma gondii (also cause cysts and calcifications)

Virus:

Cytomegalovirus (see Dr. Hermel's notes)

Non sporing Anaerobic Bacteria



You suspect an anaerobic infection when:

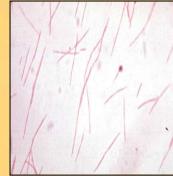
- The drained abscess pus is foul smelling
- Routine bacterial culture(incubated aerobically)is negative.

Constitute endogenous flora of the mouth and other mucosal surfaces.

Common anaerobes encountered:

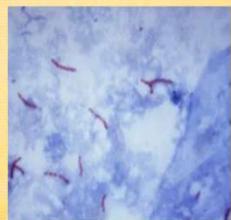
- Prevotella(Gram negative coccobacilli)
- Bacteroides (Gram negative bacilli)
- Fusobacteria (Gram negative fusiform bacilli)

Anaerobes lack Superoxide dismutase and Catalase enzymes



Gram stain showing fusiform bacilli of Fusobacteria

Microbes causing brain lesions Quick recap

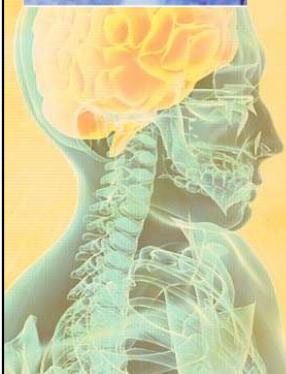


Mycobacterium tuberculosis (*Bacteria*)

M.tuberculosis is an acid-fast organism that can be stained by Ziehl Neelsen stain and is grown on Lowenstein Jensen medium.

Molecular tests- for more rapid results:

- **GeneXpert MTB/RIF assay**
- Role for **Metagenomic Next-Generation Sequencing (mNGS)**.



Cryptococcus neoformans is a yeast(fungus) can cause brain abscess/ cysts and intracranial calcifications.



Rhino-Ocular-Cerebral Mucormycosis (ROCM)

- Caused by saprophytic fungi such as Rhizopus and Mucor
- These fungi have ribbon-like, aseptate hyphae and form hyphae at 90-degree angles. They also form conidia



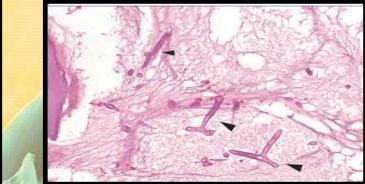
Mode of Infection- Inhalation of conidia



Mucor with hyphae and conidia



Seen in immunocompromised patients or in diabetics with ketoacidosis/ in patients on steroids
C/F: Headache, orbital cellulitis, cranial nerve palsies, coma and death



Tissue biopsy Hand E stain showing right angled branching of Mucor

Diagnosis- Tissue biopsy and fungal stain/ KOH preparation
Treatment: Surgery, Amphotericin B and control of underlying condition



Fungal infection- Mucormycosis

The emergence of another global outbreak during the COVID pandemic...

Most cases reported from India, Egypt, Iran, Mexico and a few from US, UK, Spain and France



Photo credit- Dr. V. Gore, M.G.M.Medical College and Hospital, Navi Mumbai, India

COVID-19 and Fungi: A Nightmare in the Making
India's "black fungus" crisis signals a global problem
INTERVIEW BY ANNALIES WINNT | JUNE 1, 2020

As India battles a devastating wave of COVID-19 cases, another crisis is waiting in the wings that could far outlast the pandemic—in the form of a chronic fungal disease that kills slowly and is extraordinarily difficult to treat.

A 52-yr-old male patient presented to the Ophthal OPD with complaints of redness in his eyes and loss of vision a month after he suffered from COVID 19 infection. He had received steroid therapy in addition to remdesivir. He was diabetic and hypertensive for 9 years with a recent HbA1C level of 8.4.

Patient underwent orbital exenteration of the right eye with debridement. The tissue biopsy showed histopathological and microbiological evidence of *Mucor spp.* He was treated with Amphotericin B and recovered in a few months with residual loss of vision.

COVID-19 ASSOCIATED MUCORMYCOSIS: A CASE SERIES REPORT AND AN UMBRELLA REVIEW

Pai C^{1*}, Utamsing S¹, Bayardorj D¹ Harugop A² and Gore V³

¹*Touro University College of Osteopathic Medicine, California, USA,*
²*ENT Department, Jawaharlal Nehru Medical College and Hospital, Belgaum, India*
³*Ophthalmology Department, Mahatma Gandhi Mission Medical College and Hospital, Navi Mumbai, India*

Abstract: The emerging epidemic of COVID-19 Associated Mucormycosis(CAM) has been recognized as a significant global public health threat. India accounted for majority of the globally detected CAM cases especially during the second wave of the pandemic in 2021. A severe form of invasive CAM called Rhino-orbital-cerebral mucormycosis (ROCM) led to high mortality and morbidity especially in COVID patients with predisposing factors causing immunosuppression such as diabetes mellitus, malignancies, and steroid therapy. This study was carried out to describe the demographic features as well as analyze the comorbidities and outcomes of patients diagnosed with CAM and to provide an umbrella review of published global systematic reviews on CAM with special reference to ROCM. In this case series report, we have noted the findings and outcomes of 12 COVID patients with CAM treated at two different tertiary care hospitals in India. All were males, with average age of 54.25 years. 66.6% had invasive ROCM and 91.7% had poorly controlled diabetes. All received liposomal amphotericin B, 58.3% underwent surgical interventions and the mortality rate was 33.3%. We also conducted an umbrella review of systematic reviews reported from 2020-2022. PubMed, Embase, Scopus and Google scholar databases and the PRISMA 2020 checklist were used to refine retrieval and review based on our study criteria. Common patterns were noted regarding the predisposing factors and treatment outcomes. Good glycemic control, the regulated use of steroids, proper decontamination of oxygen cylinders and the hospital environment as well as avoidance of overzealous use of steam inhalation have been proposed as important measures to control this epidemic.

Keywords: COVID-19, Rhino-Orbital-Cerebral Mucomycosis (ROCM), Diabetes Mellitus (DM).

BRAIN ABSCESS



- **PATOGENESIS:**

- Direct implantation of organisms (trauma)
- Local extension from adjacent foci (mastoiditis, paranasal sinusitis)
- Hematogenous spread (primary site of inflammation in the heart, lungs, bones or after tooth extraction).

- **PREDISPOSING CONDITIONS:**

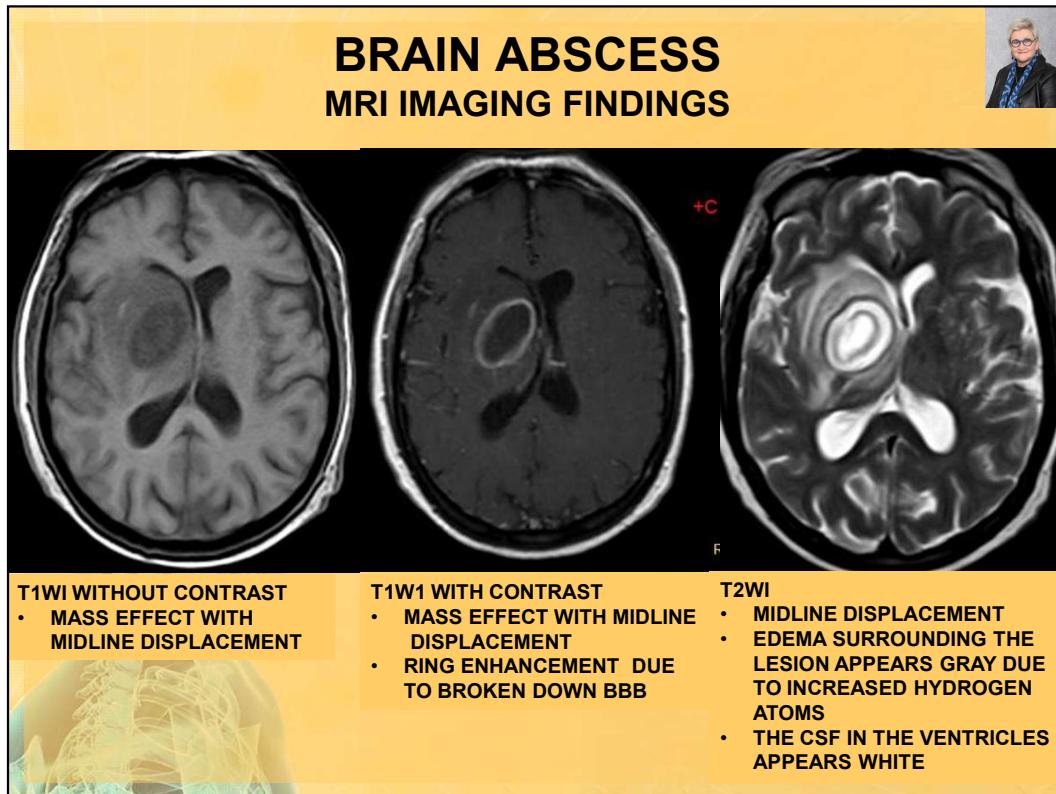
- Acute bacterial endocarditis
 - Produces multiple abscesses
- Congenital heart disease
 - Right-to-left shunting with loss of filtration of organisms from the blood by the lungs
- Chronic pulmonary sepsis
 - Bronchiectasis
 - Immunosuppression

- **MOST COMMON ORGANISMS:**

- Streptococci and staphylococci in NON-immunosuppressed patients
- Multiple organisms in immunosuppressed patients



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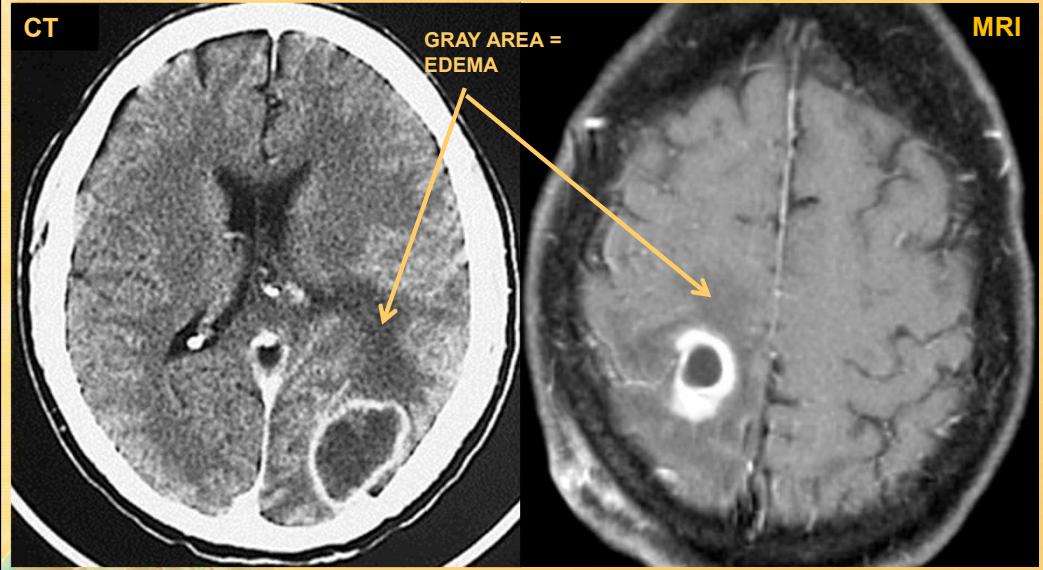


Left: T1WI without contrast enhancement: Cerebral abscess deep in the right hemisphere at the level of the thalamus causes a marked mass effect with midline shift.

Middle: T1WI with contrast shows a ring of enhancement resulting from broken blood brain barrier due to leaky vessels. Note that the edema (the gray area around the abscess) does not enhance.

Right: T2WI demonstrates the area of edema. The possibility of encephalitis in this area can not be fully ruled out. The T2 mainly shows the presence of fluid (more hydrogen atoms). Therefore CSF appears white on T2WI.

BRAIN ABSCESS RING ENHANCEMENT



RING ENHANCEMENT IS DUE TO LEAKY VESSELS AROUND THE ABSCESS CAVITY. 31

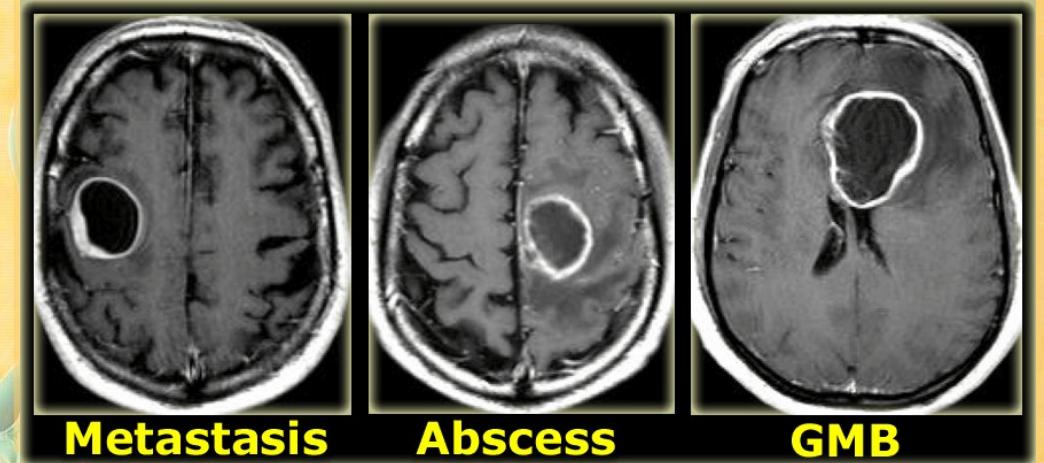
Left: CT with classic configuration of a thin-walled cerebral abscess with ring enhancement.

Right: MRI with “ring” contrast enhancement. The differential diagnosis would include abscess vs. a brain tumor (primary or metastatic). Note the surrounding edema in both studies. On CT this is a low attenuation (darker area extending anteriorly), and in the MRI exam on T1WI (T1 weighted Image) it is also darker gray. (The edema would be brighter on a T2 WI).

RING ENHANCEMENT ON CONTRAST CT



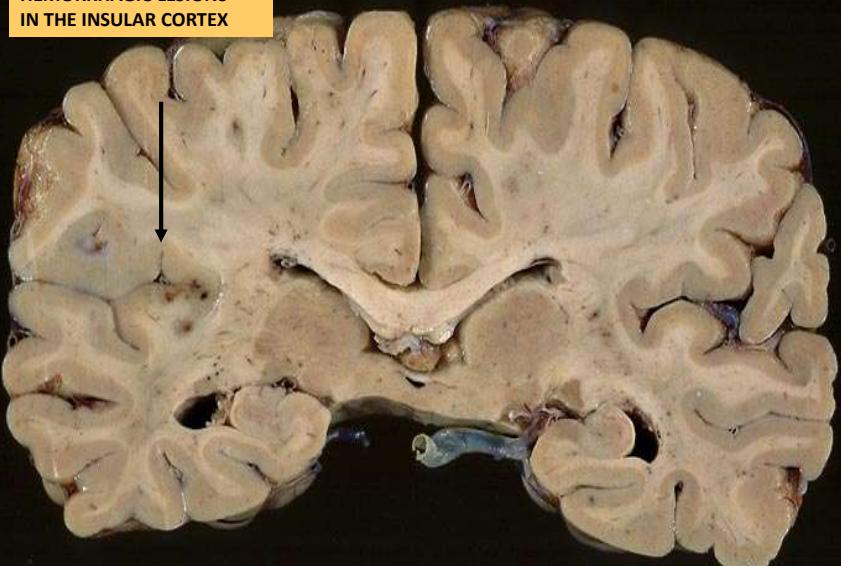
- YOU CANNOT TELL THE DIFFERENCE BETWEEN METASTASIS, ABSCESS AND BRAIN TUMOR
- ALL HAVE BROKEN BLOOD-BRAIN BARRIER BECAUSE OF LEAKY ABNORMAL VESSELS



PATHOGENESIS OF BRAIN ABSCESES: SEPTIC EMBOLI DUE TO BACTERIAL ENDOCARDITIS



HEMORRHAGIC LESIONS
IN THE INSULAR CORTEX

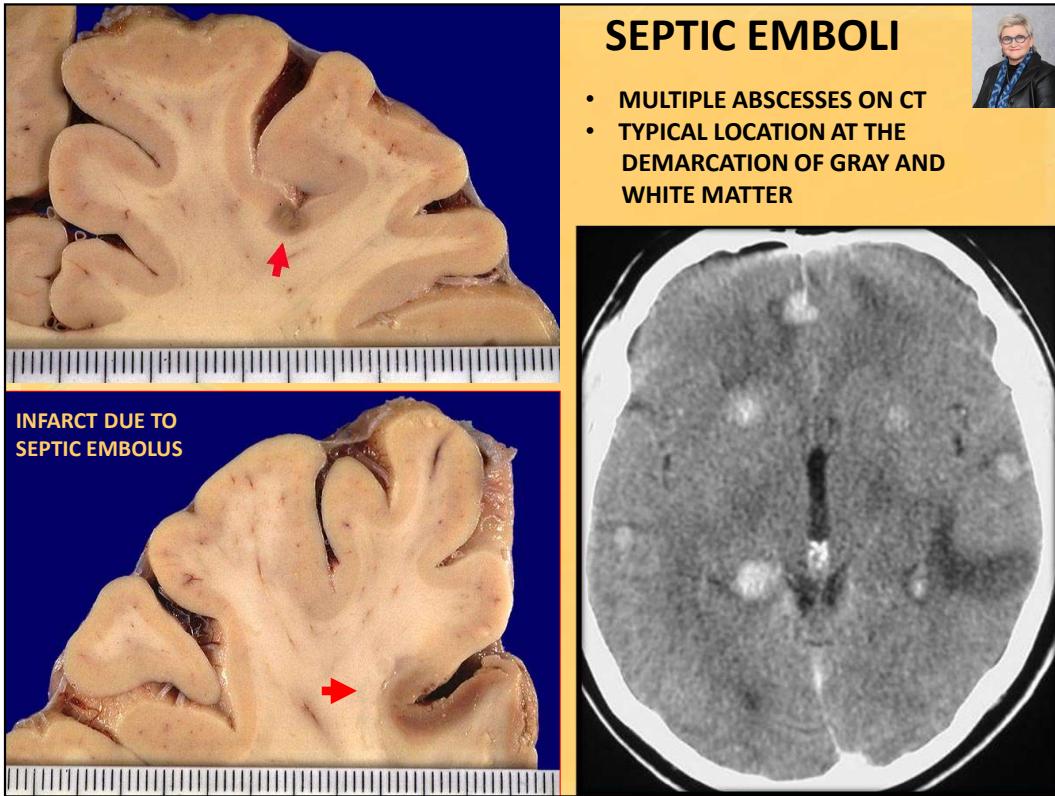


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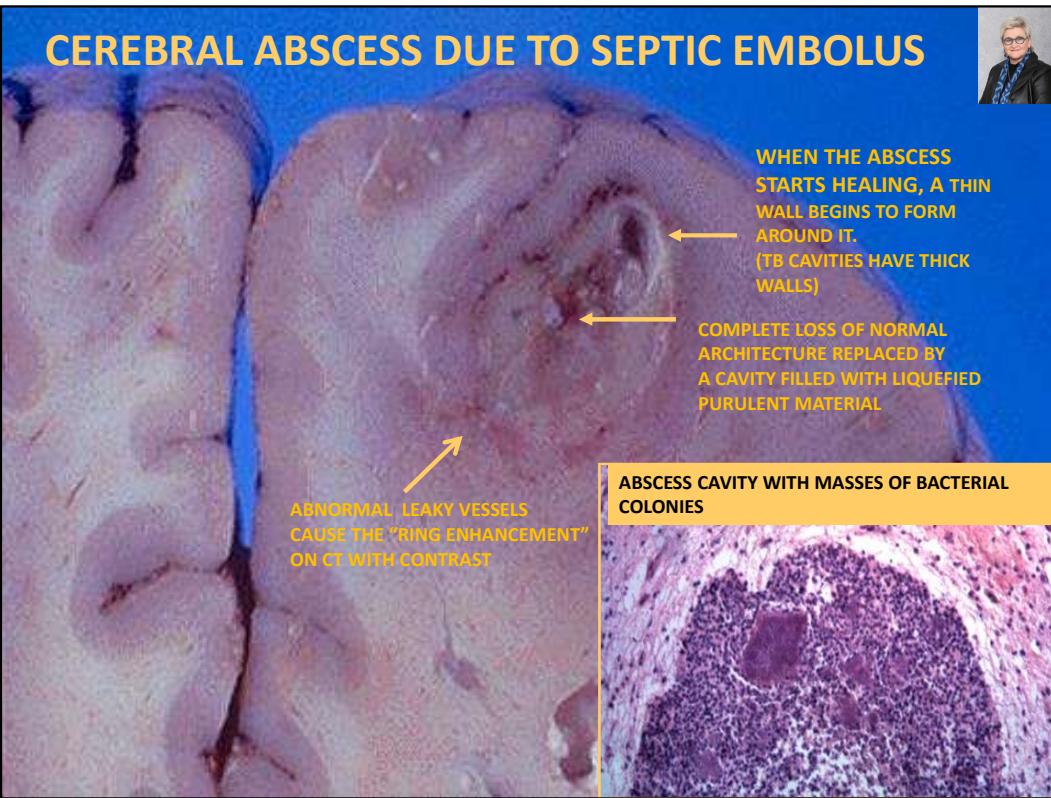
75 y o man, parietal lobe. **Diagnosis:** Septic lesion in the left insular cortex.

Description: Small round hemorrhagic lesions in the left insular cortex.

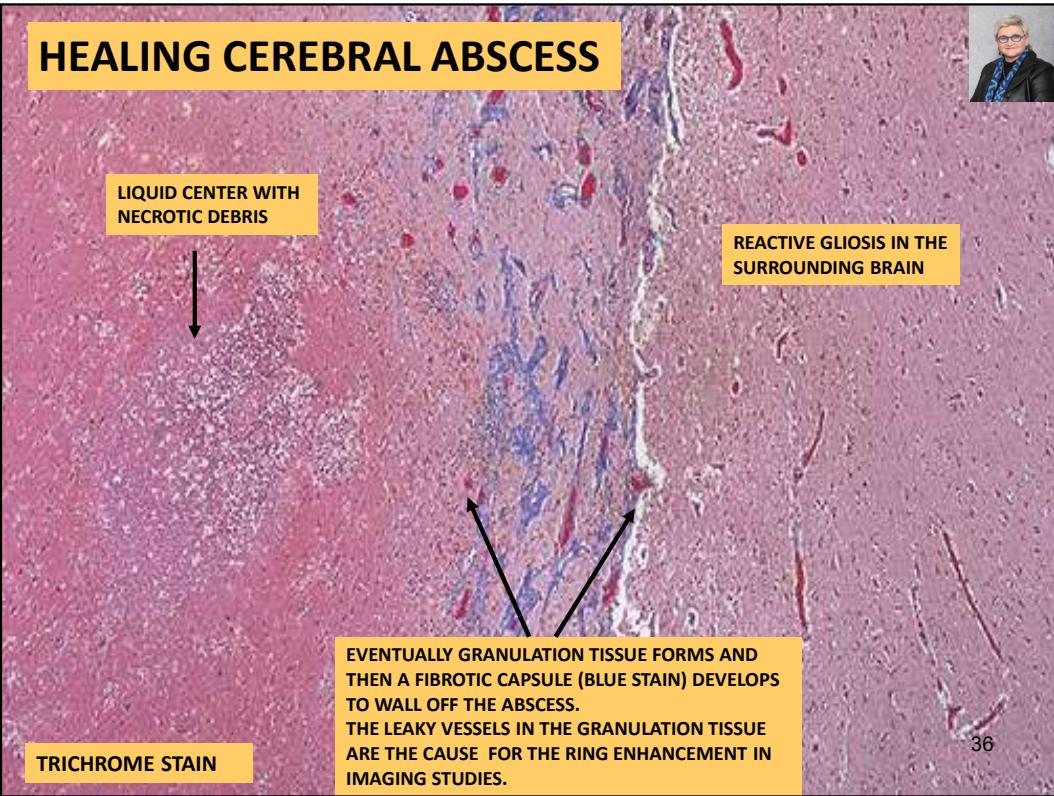
Clinical findings: Endocarditis.



64 y o man. Frontal lobe. **Diagnosis:** Septic embolic lesion of endocarditis.
Description: Round necrotic lesion in the area of an occluded vessel.
CT with contrast enhancement shows multiple lesions – most consistent with multiple embolic abscesses (radiologic differential would include multiple metastasis).



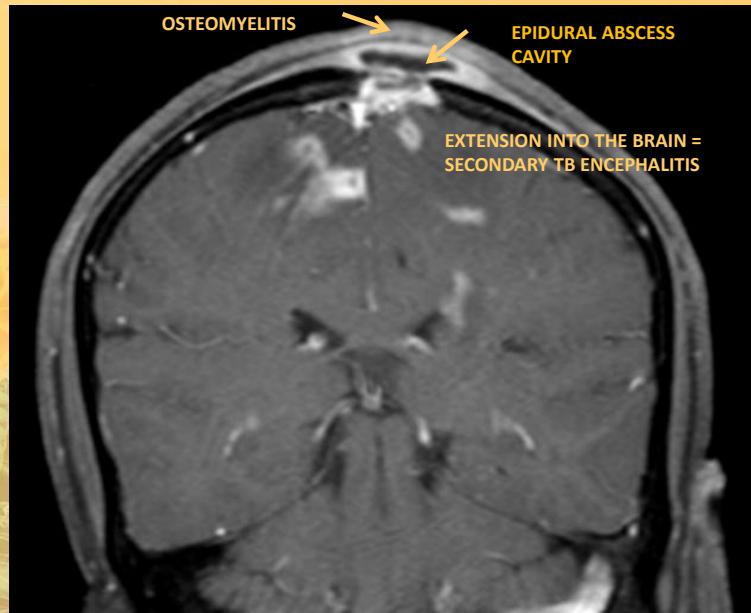
Diagnosis: Cerebral abscess: liquefactive center with yellow pus surrounded by a thin wall. Abscesses usually result from hematogenous spread of bacterial infection, but may also occur from direct penetrating trauma or extension from adjacent infection in sinuses.



Light blue connective tissue in the wall of an organizing cerebral abscess. Normal brain is on the right and the center of the abscess at the left. Stain: Trichrome.



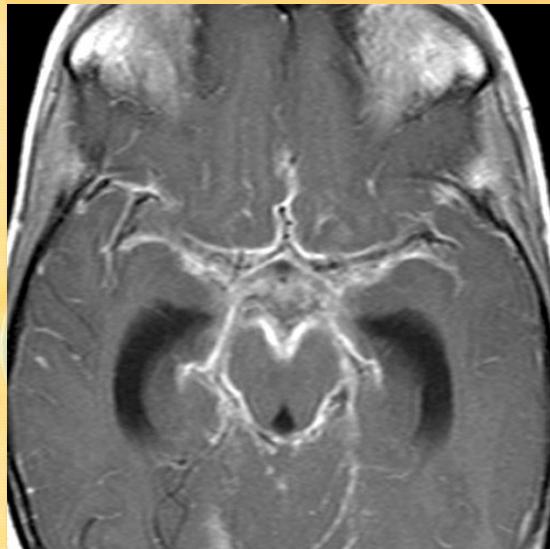
EPIDURAL ABSCESS FROM TUBERCULOUS OSTEOMYELITIS OF SKULL



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Patient with a TB osteomyelitis of the skull had an extension into the epidural space and a secondary invasion into the brain causing encephalitis.

TUBERCULOUS LEPTOMENINGITIS



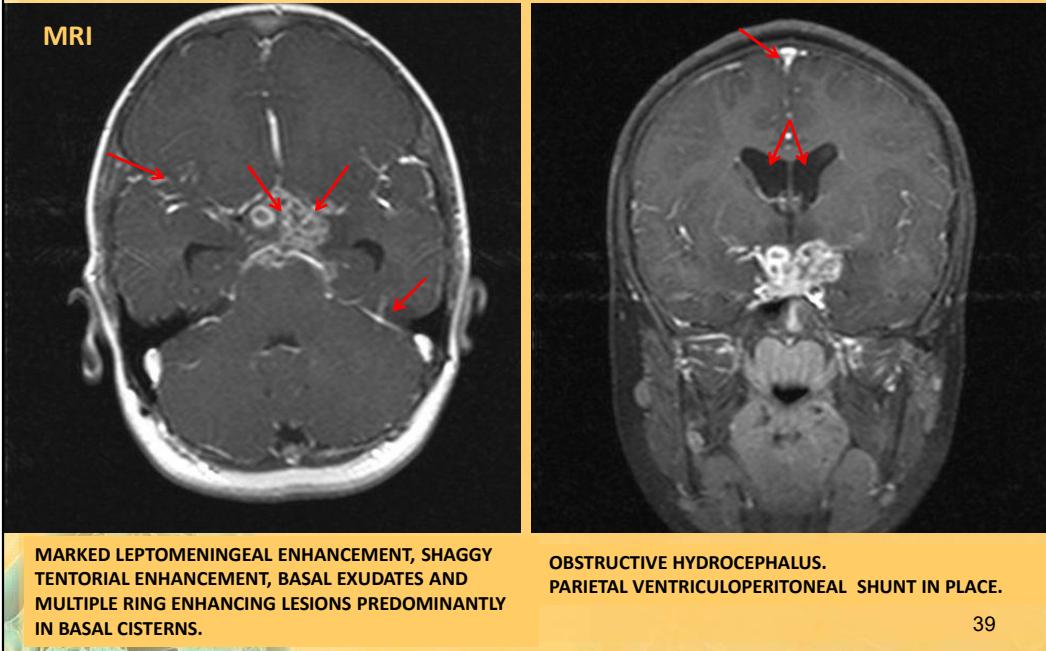
LEPTOMENINGITIS WITH A TYPICAL PATTERN OF BASAL AND CISTERNAL ENHANCEMENT



HYDROCEPHALUS IS A TYPICAL FINDING DUE TO MENINGEAL FIBROSIS AND IMPAIRED ABSORPTION OF THE CSF FROM THE ARACHNOID GRANULATIONS.

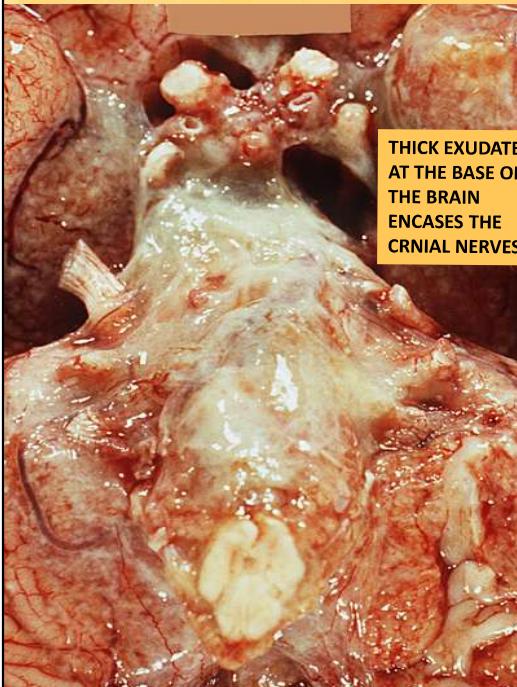
Leptomeningitis with typical pattern of basal and cisternal enhancement. Hydrocephalus is a typical finding due to fibrosis and impaired absorption of the CSF from the arachnoid granulations.

TB MENINGITIS WITH TUBERCULOMAS



MRI of the brain of an 11 year old female who presented with fever, altered sensorium and seizures over a six week period, reveals marked leptomeningeal enhancement, shaggy tentorial enhancement, enhancing basal exudates and multiple conglomerate ring enhancing lesions predominantly in basal cisterns. Obstructive hydrocephalus is also noted, with a right sided parietal VP shunt in situ.

TUBERCULOUS LEPTOMENINGITIS NECROTIZING GRANULOMATOUS INFLAMMATION

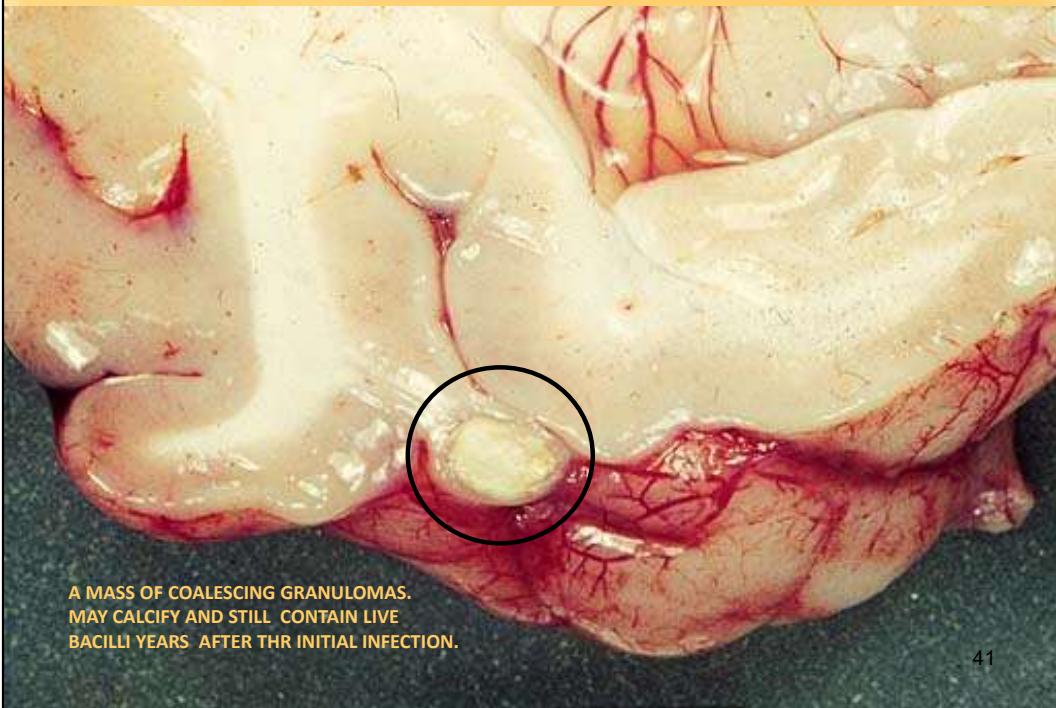


NECROSIS
(CASEOUS ON GROSS EXAMINATION)

CLASSIC TB GRANULOMA:
A RIM OF EPITHELOID CELLS AND LYMPHOCYTES SURROUNDS THE NECROSIS.
NOTE MULTINUCLEATED LANGHANS-TYPE GIANT CELLS.
THE SURROUNDING BRAIN TISSUE IS GLIOTIC.

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OLD TUBERCULOMA



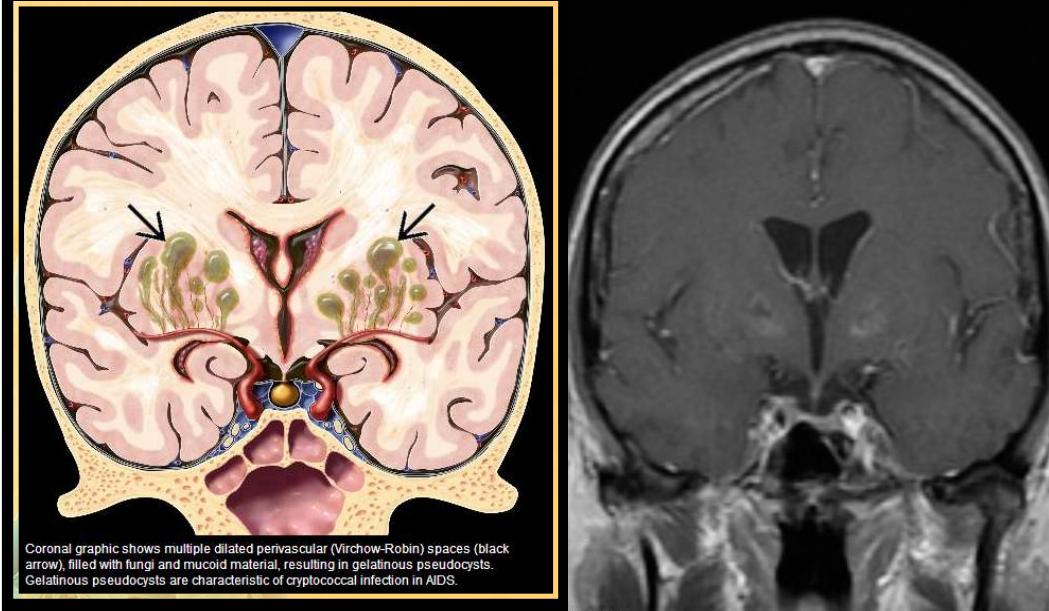
A MASS OF COALESCING GRANULOMAS.
MAY CALCIFY AND STILL CONTAIN LIVE
BACILLI YEARS AFTER THE INITIAL INFECTION.

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CRYPTOCOCCUS NEOFORMANS



- Dilated perivascular Virchow-Robin spaces
- Gelatinous pseudocysts in basal ganglia



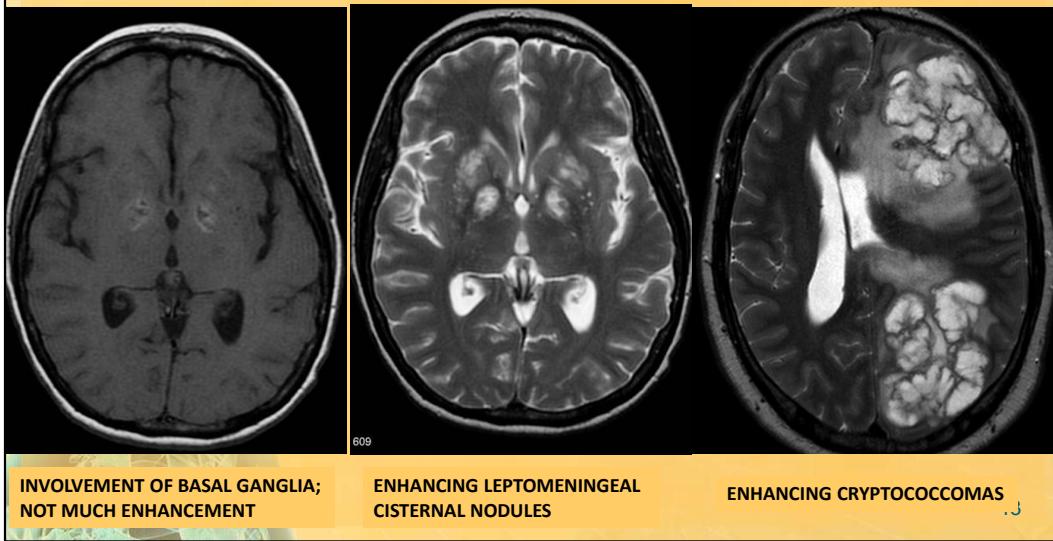
- Typically results from hematogenous spread from the lungs (which is usually the primary site).
- In HIV/AIDS patients cryptococcal infection of the CNS usually occurs when the CD4+ count drops below 100 cells/ μ L.
- The disease can have either meningeal (primary manifestation) or parenchymal involvement.
- With meningeal involvement, a grayish, mucinous exudate accumulates over the involved brain surface.
- CNS manifestations: meningitis, cryptococcomas, gelatinous pseudocysts, miliary parenchymal nodules

CRYPTOCOCCUS NEOFORMANS



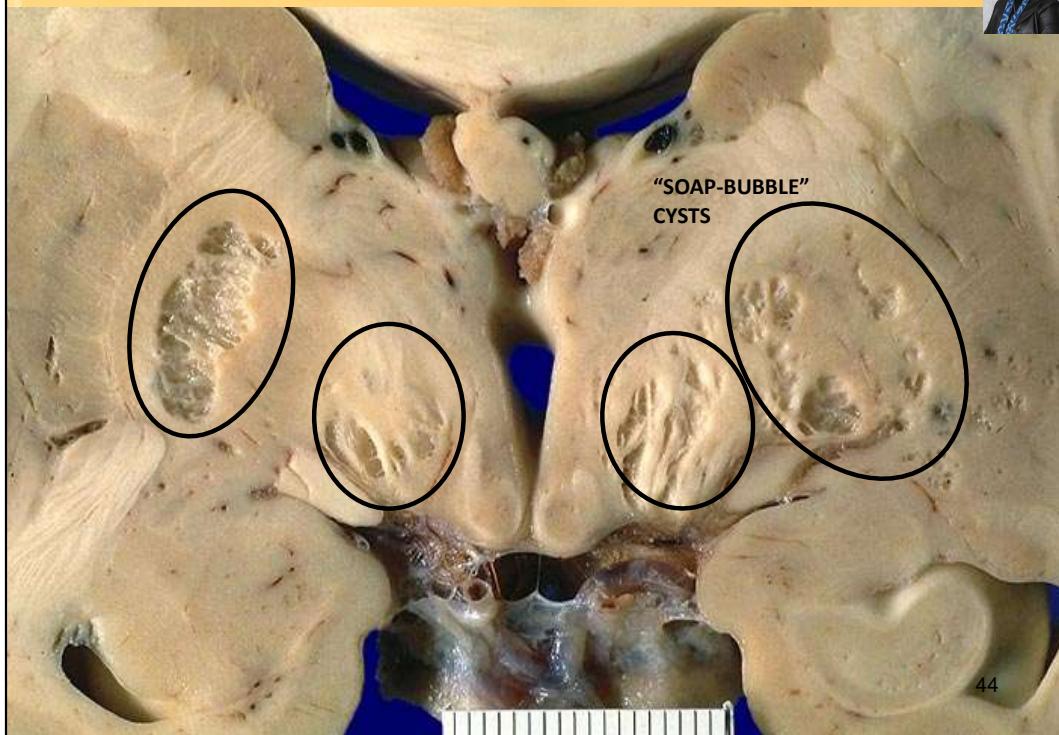
TOP DIFFERENTIAL DIAGNOSES:

- Acquired toxoplasmosis
- Tuberculosis
- Primary CNS lymphoma

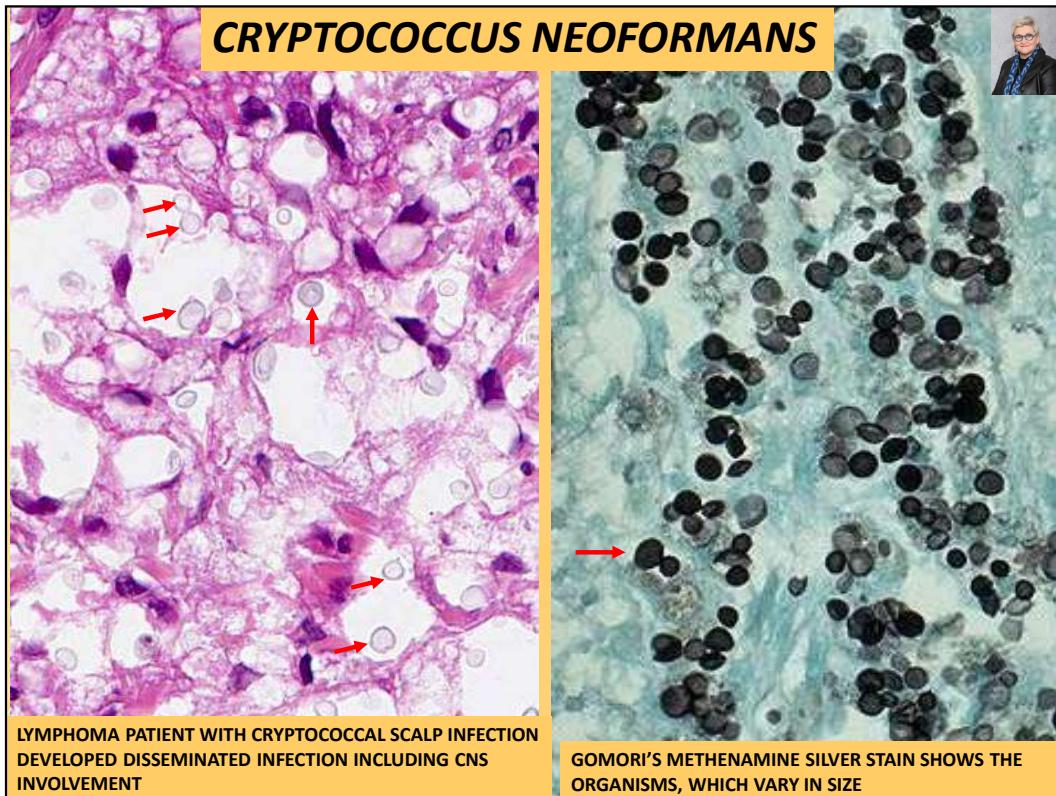


- Dilated perivascular spaces in deep gray nuclei of an AIDS patient
- Often no enhancement
- Degree of enhancement depends on the cell-mediated immunity of the host
- Miliary or leptomeningeal enhancing nodules and gelatinous pseudocysts may be present
- Cryptococcoma: ring-like or solid enhancement
- Dilated perivascular spaces in AIDS patients → consider Cryptococcal infection
- 4 imaging patterns: Miliary enhancing parenchymal nodules, leptomeningeal cisternal nodules, gelatinous pseudocysts, cryptococcomas,

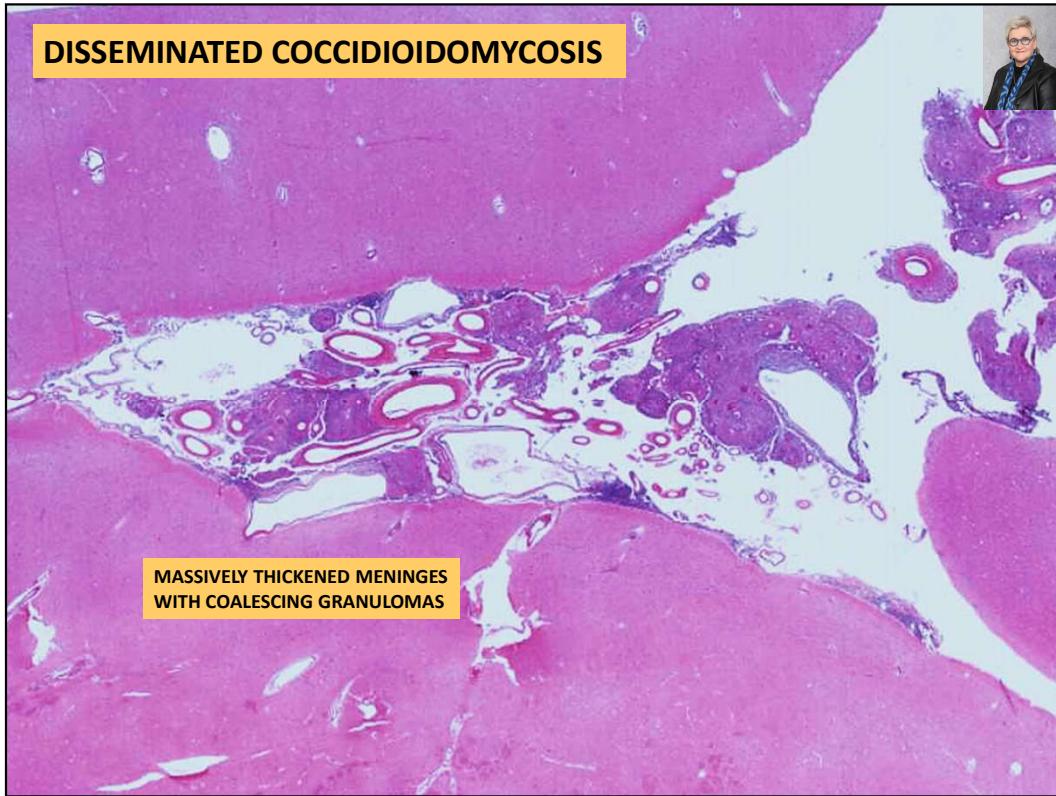
CRYPTOCOCCAL ENCEPHALITIS IN HIV



32 y o man. **Diagnosis:** Cryptococcal encephalitis. **Description:** Frontal section with basal ganglia. Numerous little cysts bilaterally destroy parts of the globus pallidus. **Additional Findings:** Grand mal seizures. Cryptococcal sepsis diagnosed 25 days ago. CSF positive for Cryptococcus. **Clinical findings:** Stage 3 HIV-Infection.

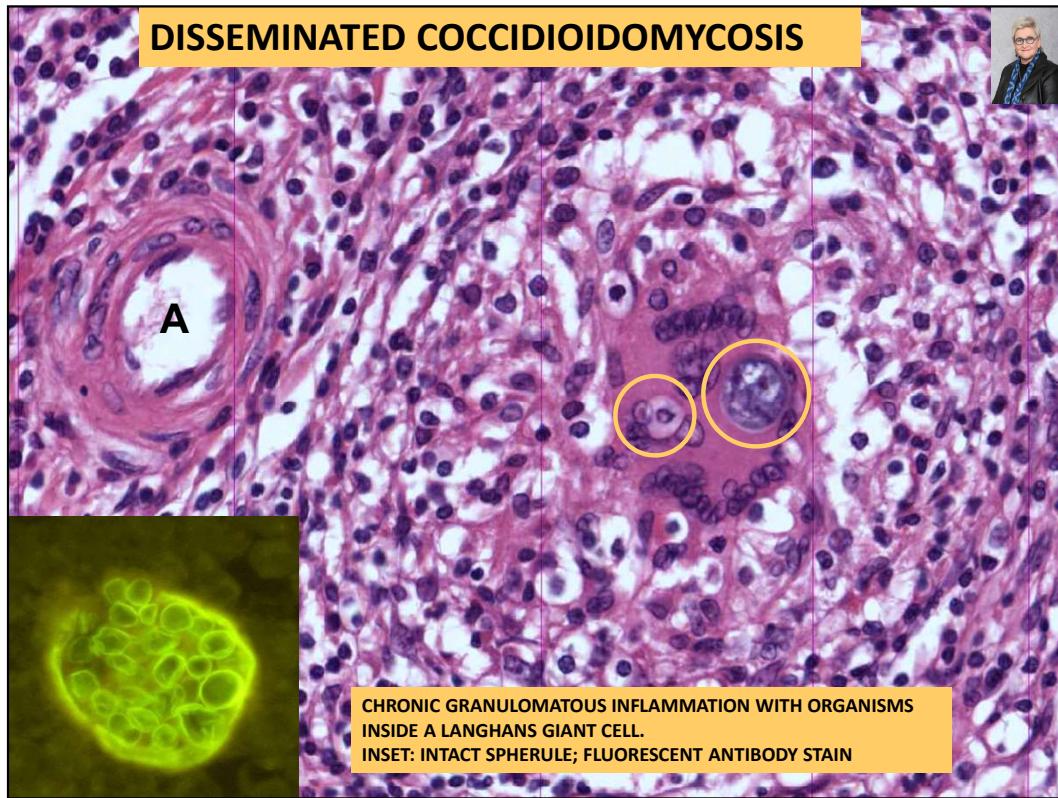


58 y o man. Scalp. **Diagnosis:** Cryptococcosis. **Description:** Massive cryptococcal infiltration in deeply ulcerated and nodular scalp lesions. **Clinical Findings:** Lymphoma patient with severe headache. **Comment:** 10% of patient with cutaneous cryptococcosis will develop hematogenous dissemination. **Stain: Left:** Hematoxylin & Eosin (H&E), **Right:** Gomori's methenamine silver.



754.svs.

- Coccidioidal meningitis (CM) is caused by *Coccidioides immitis*
- Ca 1% of the 150,000 cases diagnosed yearly will disseminate
- CM is uniformly fatal, if left untreated
- Lumbar puncture and CSF analysis is a must in any patient with suspected or previously diagnosed CM
- Diagnosis: positive serologic test or culture of CSF
- CSF has low glucose and may have very high protein content (grams instead of milligrams)
- The most common life-threatening complications of CM are hydrocephalus, CNS vasculitis, cerebral ischemia, infarction, vasospasm, and hemorrhage.
- Treatment of hydrocephalus requires a ventricular shunt into the abdominal cavity, which may lead to a secondary infection.
- Immunocompromised patients have circa 50% mortality, despite treatment.



Case 1. 754.svs. A = artery.



Diagnostic Work-Up



Rapid recognition and treatment to prevent/minimize permanent neurologic sequelae



- **CBC, blood culture, culture of abscess**
- **MRI**
 - Greatest diagnostic accuracy
 - First choice in the diagnostic process
 - Sensitivity is 90%-95%, specificity >90%
 - Gadolinium enhancement increases sensitivity for detecting spinal epidural abscess
- **CT scan**(when MRI cannot be performed). CT with IV contrast may demonstrate fluid collection in the epidural space

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. In some cases, MRI findings are indeterminate, necessitating a repeat of the study.

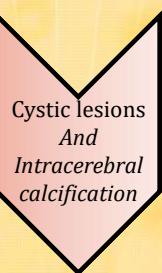
CT scanning is the procedure of choice when MRI cannot be performed. Gadolinium enhancement increases sensitivity for detecting spinal epidural abscess, even in the absence of contiguous bony infection, and enables better differentiation between abscess and surrounding neurological structures

Treatment



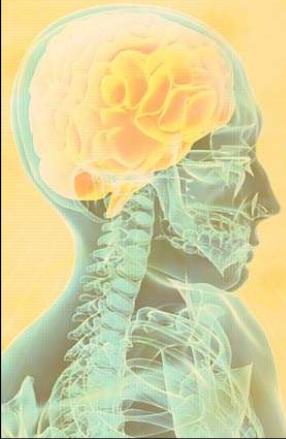
- Usually combined **medical-surgical** approach
- Emergent surgical decompression & drainage of purulent material +
- **Empirical antibiotic therapy** (Need abx with adequate CNS penetration)
 - Coverage of gram-positive cocci, particularly staphylococci (including MRSA), and gram-negative bacilli
 - **Vancomycin**
 - **Third- and fourth-generation cephalosporins** and meropenem
- *Additional coverage may be needed if some of the less-common etiologic agents are suspected*
 - *Mycobacterium species & fungi in immunocompromised*
- **Always tailor coverage once culture data are available**





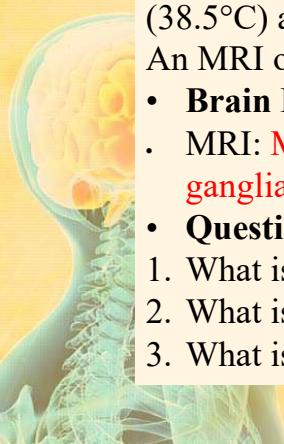
Parasites associated with Intracranial Lesions

- *Toxoplasma gondii* (parasite)
- *Taenia solium*-*Neurocysticercosis* (parasite)





Case vignette



- A 45-year-old man with a history of untreated HIV infection presents with a 1-week history of **headache, fever, confusion, and right-sided weakness**. His **CD4 count is 50 cells/ μL** . On examination, he is febrile (38.5°C) and disoriented, with **right-sided hemiparesis**. An MRI of the brain is obtained.
 - **Brain Imaging:**
 - MRI: **Multiple ring-enhancing lesions in the basal ganglia and cerebral cortex with surrounding edema.**
- **Questions:**
 1. What is the most likely diagnosis?
 2. What is the causative organism?
 3. What is the recommended initial treatment regimen?

Answers:

1. The most likely diagnosis is **cerebral toxoplasmosis**.
2. The causative organism is **Toxoplasma gondii**.
3. The first-line treatment includes **pyrimethamine, sulfadiazine, and leucovorin**.



Toxoplasma gondii- Toxoplasmosis

- Obligate intracellular protozoal parasite
- Found worldwide; most infections are asymptomatic. (> 11% of the population over 6 years of age are infected with T. gondii in the United States).
- Definitive host -CAT. Intermediate host- other animals and human beings.
- Serious infection for immunocompromised (brain abscess, calcified lesions, encephalitis) and fetus in utero (congenital toxoplasmosis)

★ Modes of transmission:

1. Ingestion

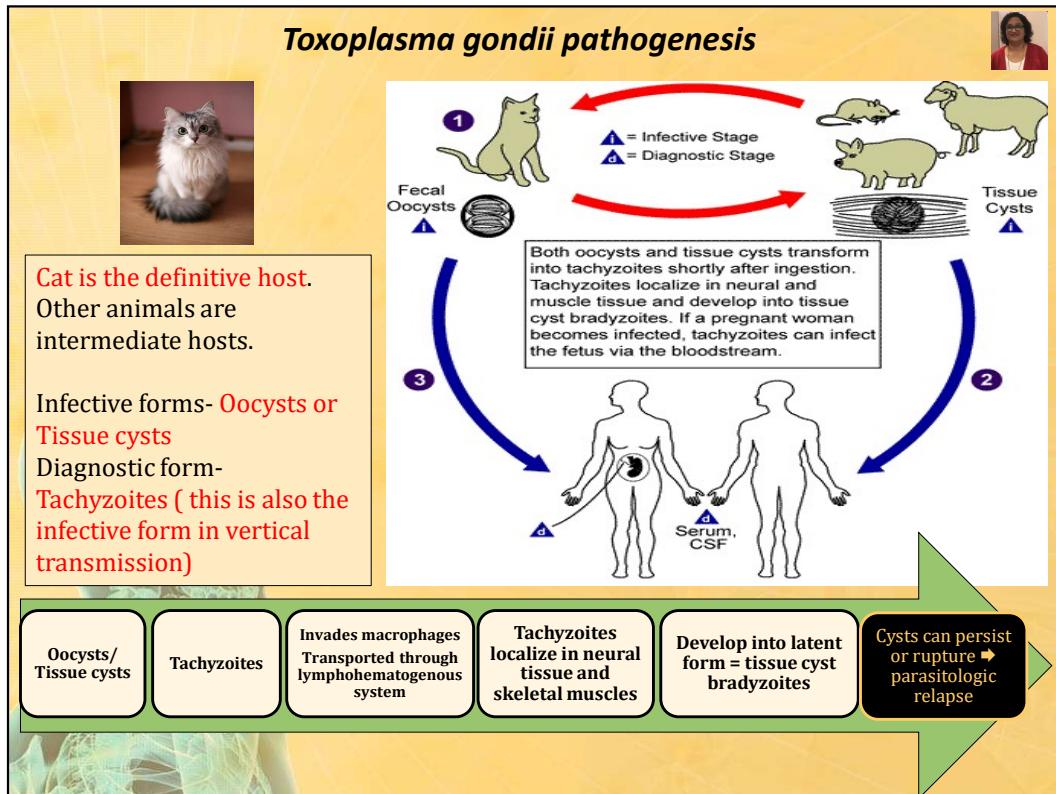
- Foodborne: Ingestion of tissue cysts via consumption of undercooked or raw meat
- Zoonotic transmission: Ingestion of oocysts via consumption of food and water contaminated with feline feces.

2. Vertical transmission: From infected mother to the fetus through the placenta.

3. Via organ transplantation or blood transfusion

1.Foodborne transmission: Ingestion of tissue cysts via consumption of undercooked or raw meat

2.Zoonotic transmission: Ingestion of oocysts via consumption of food and water contaminated with feline feces



- Cat is the definitive host.
- Oocysts passed in feces and mature into infective oocysts in environment
- Intermediate hosts (humans or other animals like pigs, hens, sheep, mice etc.) exposed to infective oocysts. Tissue cysts are formed in these hosts.



In immunocompetent hosts

- commonly asymptomatic
- may develop lymphadenopathy and/or a non-specific flu-like or infectious mononucleosis(IM)-like illness
- benign and self-limited

In immunocompromised hosts

- highly lethal disease
- toxoplasmic encephalitis = often reactivation of chronic infection
- symptoms related to location of lesions: hemiparesis, seizure, visual impairment, confusion

Congenital toxoplasmosis

If exposed before pregnancy, maternal antibodies protect the fetus

If *Toxoplasma* crosses placenta early(first trimester) ➔ Infection is very severe- intracerebral calcifications , chorio-retinitis, hydrocephaly/ microcephaly, abortion and death of fetus

If *Toxoplasma* crosses placenta later(third trimester) ➔ infection may be inapparent.

Inapparent infection left untreated cause manifestations later in life such as progressive blindness, mental disabilities, seizures, learning disabilities



Toxoplasmosis – Diagnosis

1. Serologic testing- primary diagnostic tool

- Rising or high titers of IgM indicate active infection
- Positive IgG will be seen in reactivation syndromes

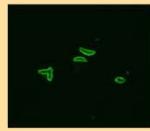
2. Molecular testing: PCR for *T.gondii* DNA in blood and body fluids.

3. Radiological diagnosis: CT / MRI show multiple hypodense areas with ring enhancing lesions in the brain.

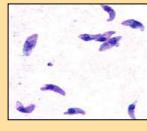
4. Biopsy- not usually performed.

Observation of parasites in body fluids or tissue biopsies

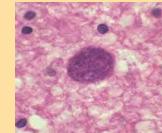
- Tachyzoites – invade macrophages (disseminating form)
- Bradyzoites – latent form within tissue cyst



Immunofluorescence antibody (IFA)



Giemsa stain of tachyzoites



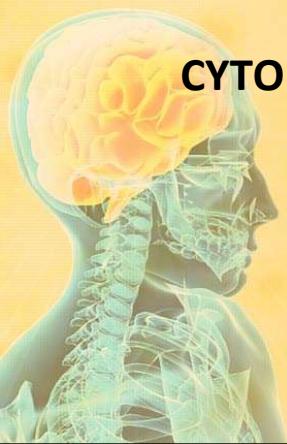
Cyst in brain tissue

Serological testing: This is the primary diagnostic method to determine infection with *Toxoplasma* by identifying IgM and IgG antibodies. IgM antibodies are usually detectable from day 5 following infection, reaching maximum levels in 1 to 2 months. IgG antibodies are detectable after 1 to 2 weeks of infection, reaching maximum levels in 3 to 6 months.



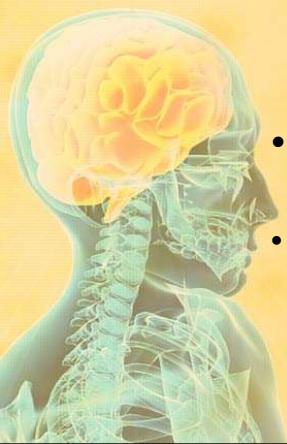
TOXOPLASMOSIS

**CNS IMAGING AND
CYTOLOGIC/HISTOLOGIC FEATURES**





TOXOPLASMOSIS IMAGING



- Multiple regions are typically affected:
- Mostly basal ganglia and corticomedullary junction, posterior fossa sometimes
- Following administration of contrast there is nodular or ring enhancement:
 - Ring enhancement is typically thin and smooth
- Double-dose delayed scan:
 - Central filling may show on delayed scans
- Calcifications:
 - Seen in treated cases
 - May be dot-like or thick and 'chunky'

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TOXOPLASMOSIS IMAGING



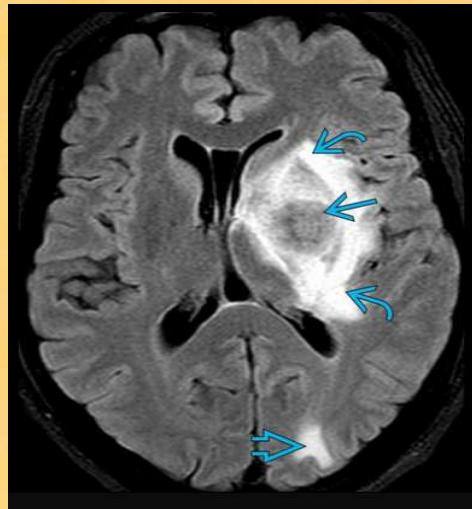
DIFFERENTIAL DIAGNOSIS:

- CNS lymphoma



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MULTIPLE RING-ENHANCING LESIONS IN BASAL GANGLIA



LARGE MASS, SUSPICIOUS FOR LYMPHOMA

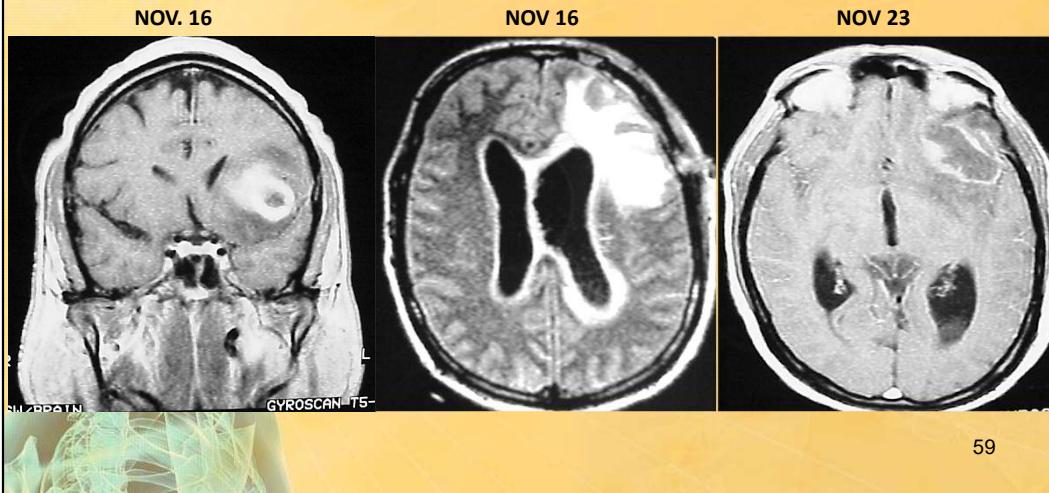
58

Differential diagnosis CNS Lymphoma

TOXOPLASMOSIS

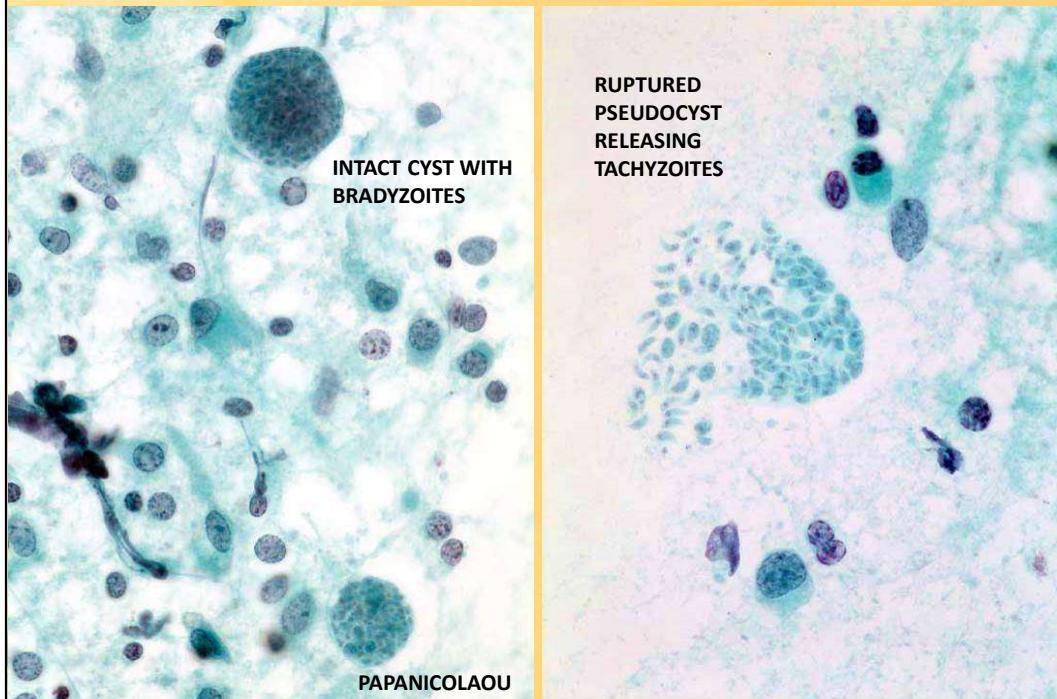


- 32 years-old AIDS patient
- Toxoplasma abscess and ependymitis with impending rupture into the ventricle
- Rupture into the ventricle 7 days later



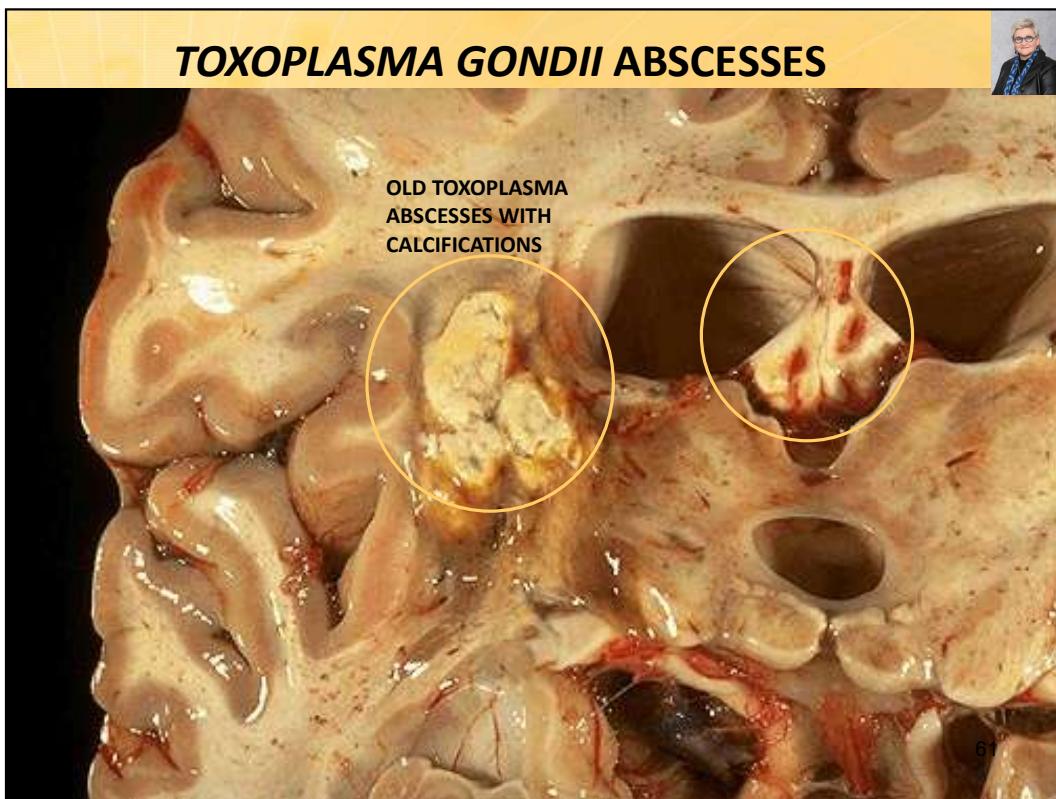
AIDS patient with toxoplasmosis on Nov 16: Toxoplasma abscess and ependymitis with impending rupture into the ventricle. Follow-up on Nov 23: Toxoplasma abscess and ependymitis with rupture into the ventricle.

TOXOPLASMOSIS: DIAGNOSTIC CSF CYTOLOGY



47 y o man. **Diagnosis:** Toxoplasmosis. **Description;** Pseudocysts with bradyzoites.

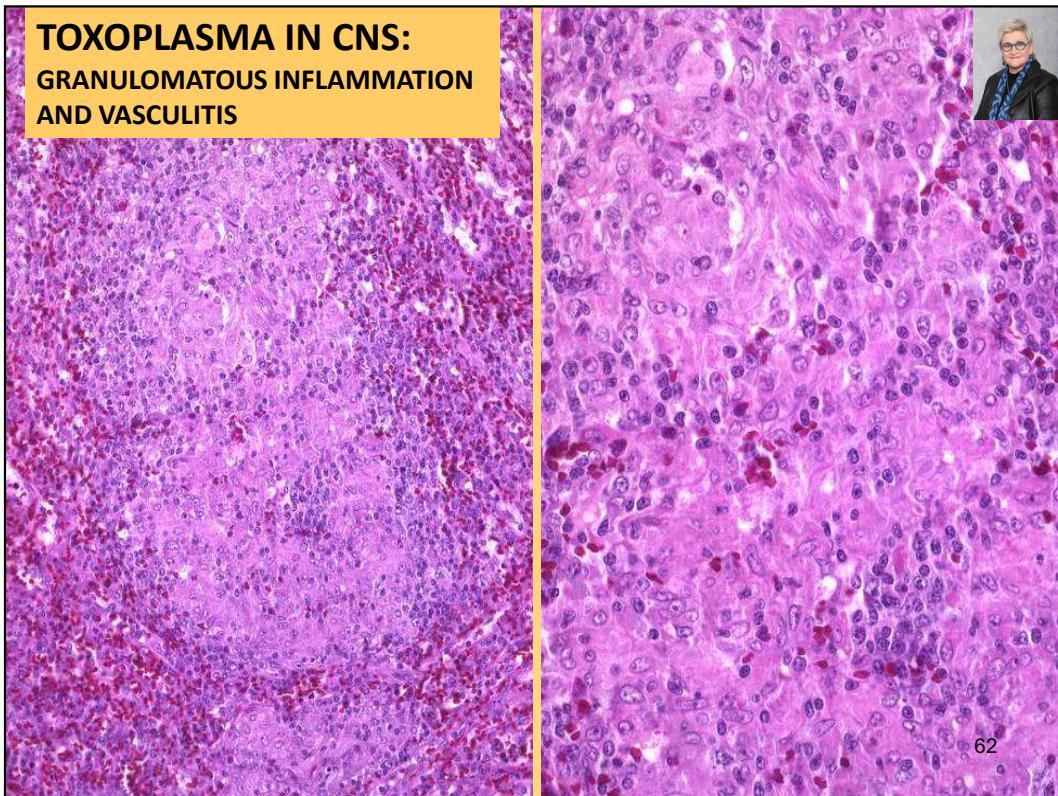
TOXOPLASMA GONDII ABSCESSES



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Toxoplasma gondii infection is most often manifested in the central nervous system. Multiple abscesses that are ring-enhancing with CT scans can be seen. Older abscesses can organize and have calcifications as shown here.

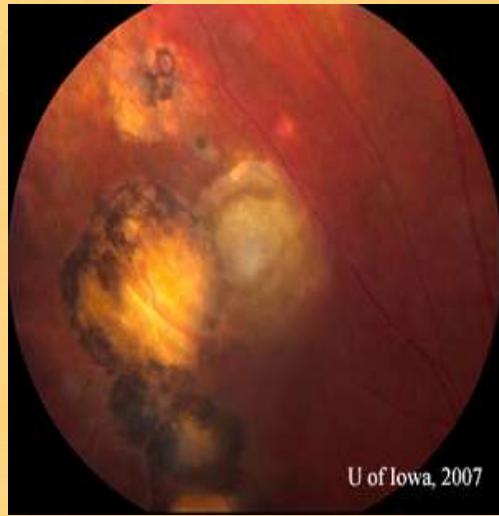
**TOXOPLASMA IN CNS:
GRANULOMATOUS INFLAMMATION
AND VASCULITIS**



TOXOPLASMA RETINITIS



U of Iowa, 2007



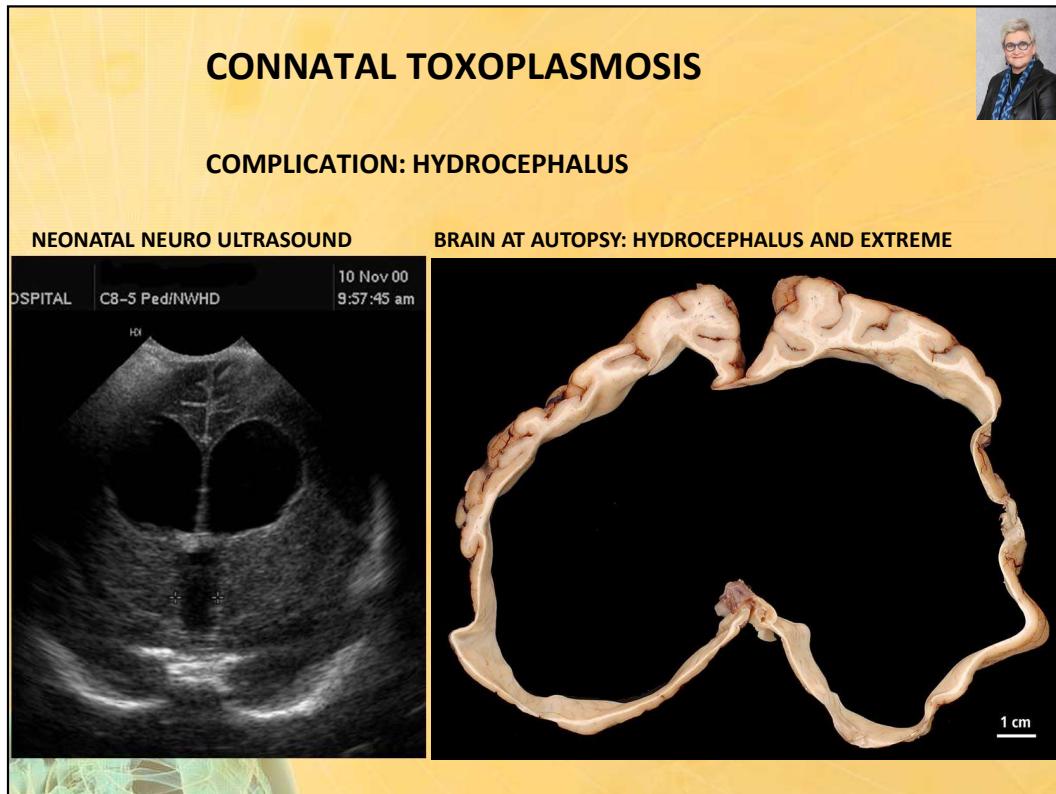
U of Iowa, 2007

THICK, PERIARTERIOLAR KYRIELEIS PLAQUES
SURROUND PERILESIONAL VESSELS

RETINAL SCARRING DUE TO TOXOPLASMA
RETINITIS

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Diagnosis: Hydrocephalus after connatal toxoplasmosis. **Description:** Massive dilatation of the ventricles.
The image on the right is from an Ultrasound performed through the anterior fontanel in a coronal plane. Note the rounding of the lateral ventricles and enlargement of the 3rd ventricle.



Toxoplasmosis – Treatment

- Indicated in all immunocompromised patients and immunocompetent patients with severe/ prolonged symptoms
- Regime-
 - Immunocompromised patients
 - Pyrimethamine + Sulfadiazine + Folinic acid(leucovorin)- 4 to 6 weeks.
 - Pregnant women
 - Spiramycin- helps reduce transmission to fetus esp when given within 8 weeks of seroconversion.
Pyrimethamine should not be used in the first trimester of pregnancy because it's teratogenic.
 - Congenitally infected newborns are generally treated with pyrimethamine, a sulfonamide, and leucovorin for 12 months.

Prophylactic anti-toxoplasma therapy is started in patients with HIV/AIDS who are *T. gondii* IgG positive with CD4 cell counts <100 cells/microL.



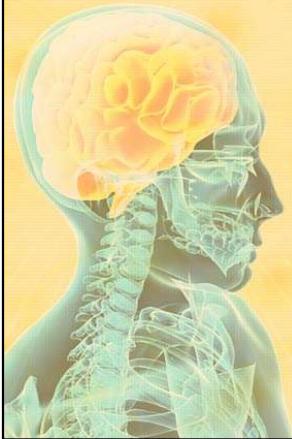
Other cystic/ calcified lesions in the brain





Neurocysticercosis

Caused by the larval forms of
***Taenia solium* (pork tapeworm)**





Case vignette



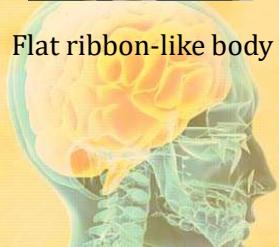
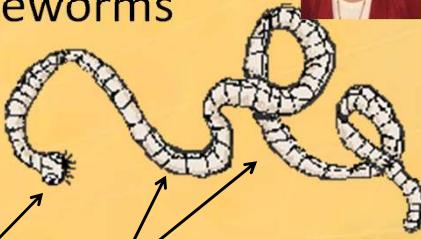
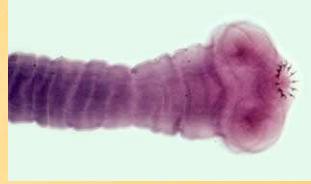
- A 13-year-old boy presents with a 3-day history of **headache, fever, and generalized tonic-clonic seizures**. He recently immigrated from a **rural area in South America**. On examination, he is febrile (38.5°C), has mild neck stiffness, and a positive Kernig's sign. An MRI of the brain is obtained.
- **Brain Imaging:**
- MRI: **Multiple cystic lesions with ring enhancement and surrounding edema in both the cerebral cortex and subcortical regions.**
- **Questions:**
 1. What is the most likely diagnosis?
 2. How does the lifecycle of the causative organism lead to neurocysticercosis?
 3. What public health measures can help prevent this condition?

Answers:

1. The most likely diagnosis is **neurocysticercosis**.
2. The lifecycle involves **ingestion of Taenia solium eggs** from contaminated food or water, leading to larvae (cysticerci) migration to the brain where they form cysts.
3. Public health measures include **improving sanitation, educating about proper cooking of pork, and treating tapeworm carriers** to prevent transmission.



Intestinal Cestodes or Tapeworms



Flat ribbon-like body
Head = scolex
Equipped with organs of attachment



Individual segments of tapeworms are the proglottids

Taenia saginata
Beef tapeworm

Taenia solium
Pork tapeworm

Diphyllobothrium latum
Fish tapeworm

Echinococcus
Hydatid tapeworm

*Other tapeworms will be taught in IS-GERD

Cysticercosis



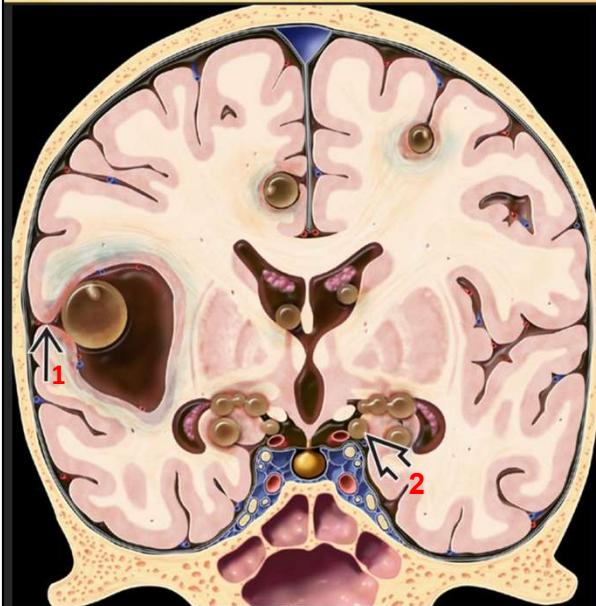
- Transmission
 - ★ • Ingestion of water or food contaminated with *Taenia solium* eggs
- Pathogenesis
 - ★ • Eggs hatch in stomach and release oncosphere
 - Oncosphere penetrate intestinal wall → circulation → travels to different tissues and develops into cysticercus
- Diagnosis – difficult
 - ★ • Demonstration of calcified cysticerci in the tissue
 - Neurocysticercosis: MRI or CT brain scans
 - Cysticerci in muscle
 - Antibody detection
- Treatment
 - ★ • Albendazole or praziquantel
 - Steroids to decrease inflammation
 - Surgical removal of cysts



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NEUROCYSTICERCOSIS



[View Full Screen Image](#)
Coronal graphic shows subarachnoid and ventricular cysts. The convexity cysts have a scolex and surrounding inflammation. Note that the inflammation around the largest cyst "seals" the sulcus and makes it appear parenchymal. Racemose cysts are multilocular, nonviable, seen in the basal cisterns and typically lack a scolex.

- Coronal graphic shows subarachnoid and ventricular cysts.
- The cysts on the convexity of the brain have a scolex and are surrounded by inflammation (arrow #1).
- The inflammation “seals” the sulcus and makes the cyst appear intraparenchymal.
- The basal cisterns contain multiloculated grape-like clusters of racemose cysts (arrow #2).
- This form of cysticercosis can be fatal.

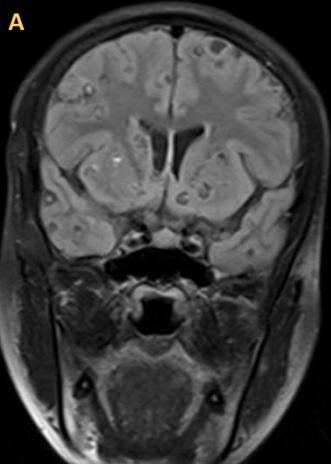
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Coronal graphic shows subarachnoid and ventricular cysts. The cysts on the convexity of the brain have a scolex and are surrounded by inflammation (arrow #1). The inflammation “seals” the sulcus and makes the cyst appear intraparenchymal. The basal cisterns contain multiloculated grape-like racemose cysts (arrow #2). This form of cysticercosis can be fatal.

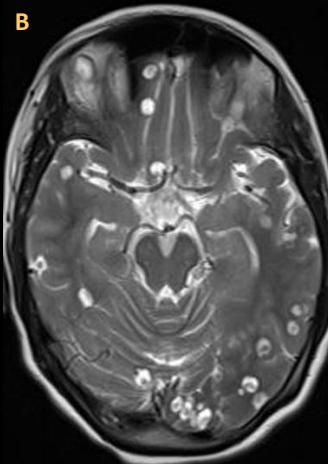
NEUROCYSTICERCOSIS



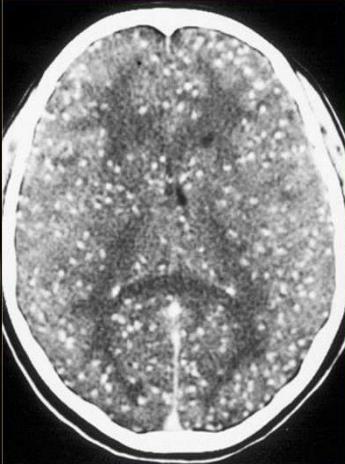
MRI CORONAL T1WI



MRI AXIAL T2WI



CT

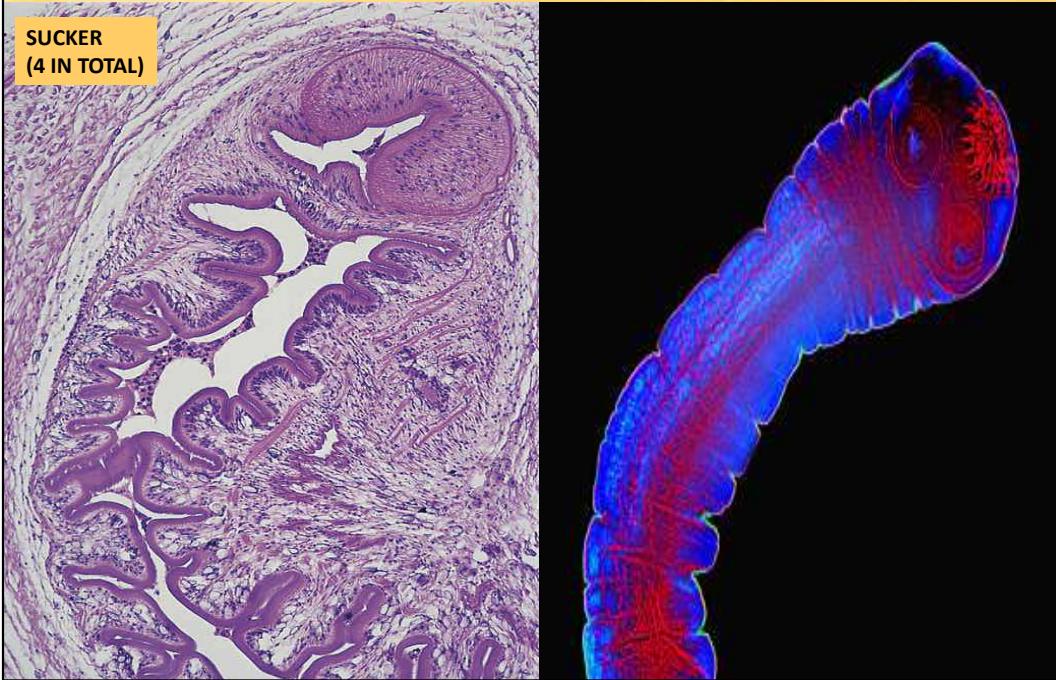


A AND B: MULTIPLE LESIONS THROUGHOUT THE BRAIN. THE PATIENT PRESENTED WITH GENERALIZED TONIC-CLONIC SEIZURES.

C: MASSIVE CYSTICERCOSIS

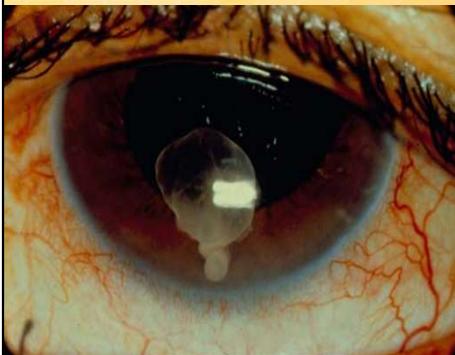
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NEUROCYSTICERCOSIS



Neurocysticercosis. The parasite's main structural features include a prominent investing tegument or 'cuticle', aggregated subcuticular cells, smooth muscle fibers, and four suckers, one of which is depicted at upper left.

CYSTICERCOSIS



CYSTICERCUS IN THE ANTERIOR CHAMBER

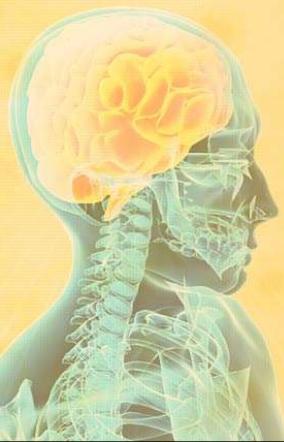
CYSTICERCOSIS CAN CAUSE BLINDNESS



- ORAL MUCOSA IS A NOT AN UNCOMMON LOCATION FOR CYSTICERCOSIS CYSTS
- MAY INDICATE DISSEMINATION TO OTHER SITES

Cysticercus in the anterior chamber of the eye. The patient had known neurocysticercosis and presented with monocular loss of vision

Toxin Mediated Infections of The Nervous System



Botulism- will be taught in Musculoskeletal infections and IS-GERD-GIT infections

Tetanus- will be taught in Musculoskeletal infections

