CCM Interhospital Grandround 24th May 2016

Spray the Holy Water

Speaker: L Lau

Chairman: FL Chow

Case Presentation

- 52-year-old lady, non-smoker, non-drinker
- Labelled Right eye optic neuritis in early December 2015
- ICU was consulted on 30/12/2015 for Plasmapharesis for demyelinating disease/ CNS infection

Timeline

Late November

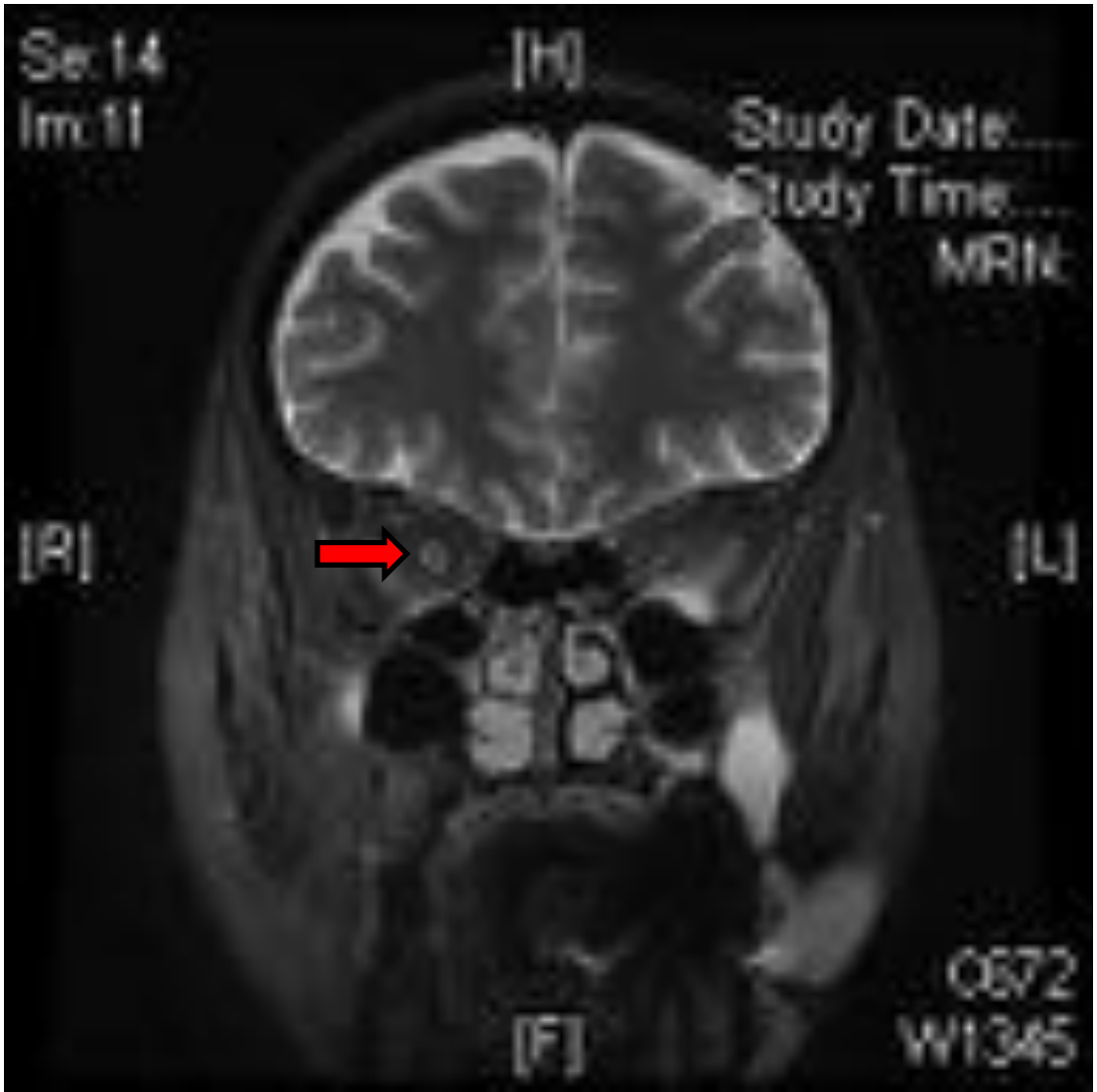
- Visited AED on 23rd, 25th, 30th for severe headache
- Admitted to KWH for severe headache for one month, radiate to neck, mainly over the right temporal region, associated with decrease vision of right eye, ESR 37
- Consulted EYE for suspected temporal arteritis, no notes traced from EYE, Discharged on 2/12/2016 given Gabapentin, Voltaren and Panadol

Timeline

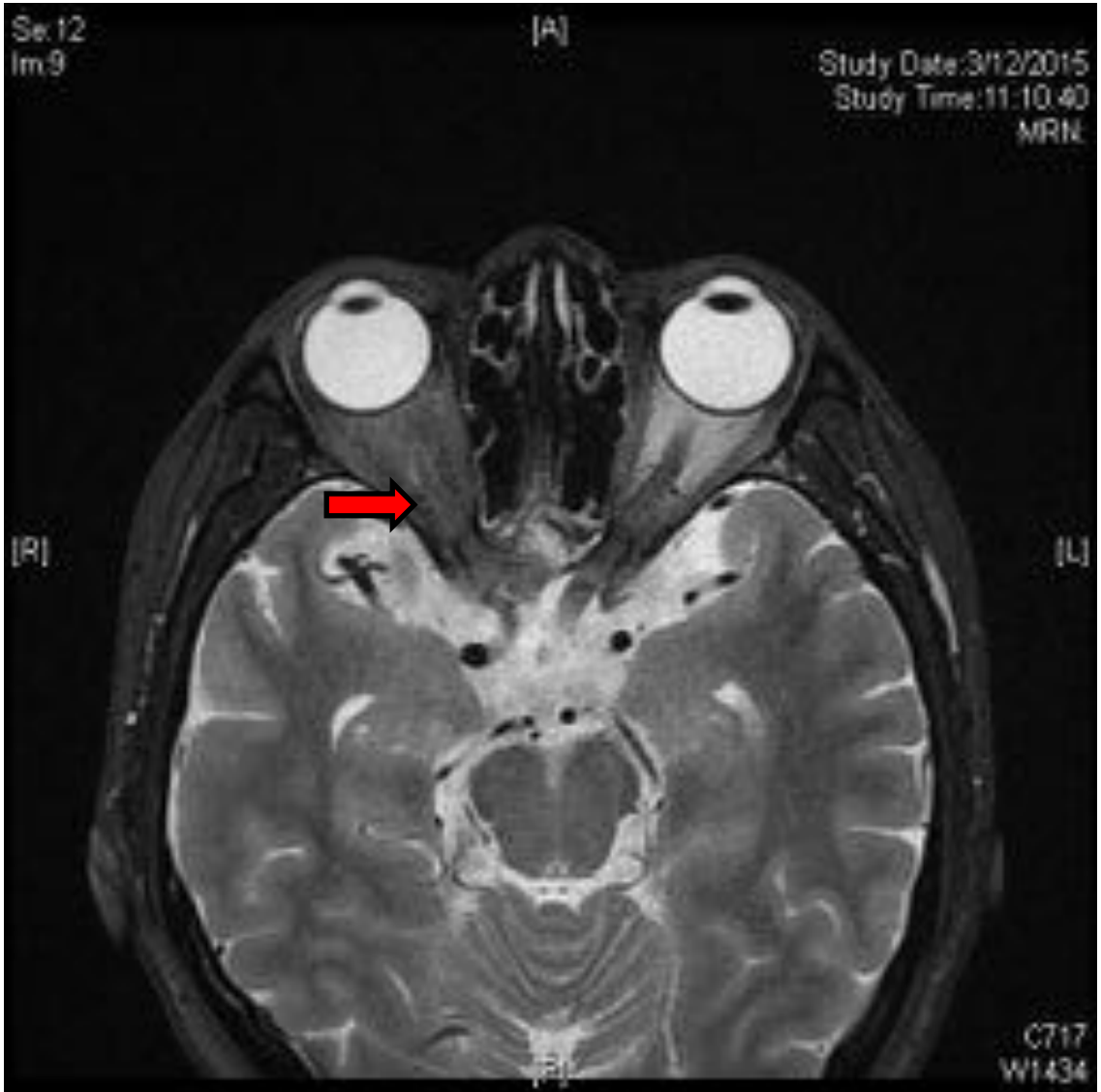
Early December

- Visited AED in CMC same day on 2/12/2016
- MRI brain done on 3/12/2016 in Private
- Clinically admitted to Eye ward on 4/12/2016, diagnosed right optic neuritis , confirmed with private MRI
- Start ONTT Methylprednisolone 250mg Q6H for 3 days and responded well
- VA recovered from 0.2 to 0.7 in 4 days, discharged on 8/12/2016
- Discharged with Prednisolone 50mg Daily

MRI T2 Coronal view on 3/12/2015



MRI T2 Transverse view on 3/12/2015



MRI brain on 3/12/2016

- The cerebral sulci are not dilated. **Two T2 hyperintense lesions are demonstrated in the left coronal radiata**. The anterior one measures 0.4 x 0.5 x 0.6cm. The posterior one measures 0.4 x 0.4 x 0.8cm. The rest of the cerebral hemispheres is unremarkable. The ventricles are not dilated. There is no subdural collection seen. Diffusion scan shows no acute cerebral ischemia. The posterior cranial fossa is unremarkable.
- Paranasal sinuses are clear. No obvious mass lesion is demonstrated in the orbits. The ocular muscles are unremarkable. **Mild swelling is noted in the right optic nerve** compared to the left side. **A rim of T2 hyperintensity is seen in the peripheral part of the nerve**. Mild contrast enhancement of right optic nerve is demonstrated. No abnormal enhancement is noted in the brain.

MRI Opinion from Private radiologist

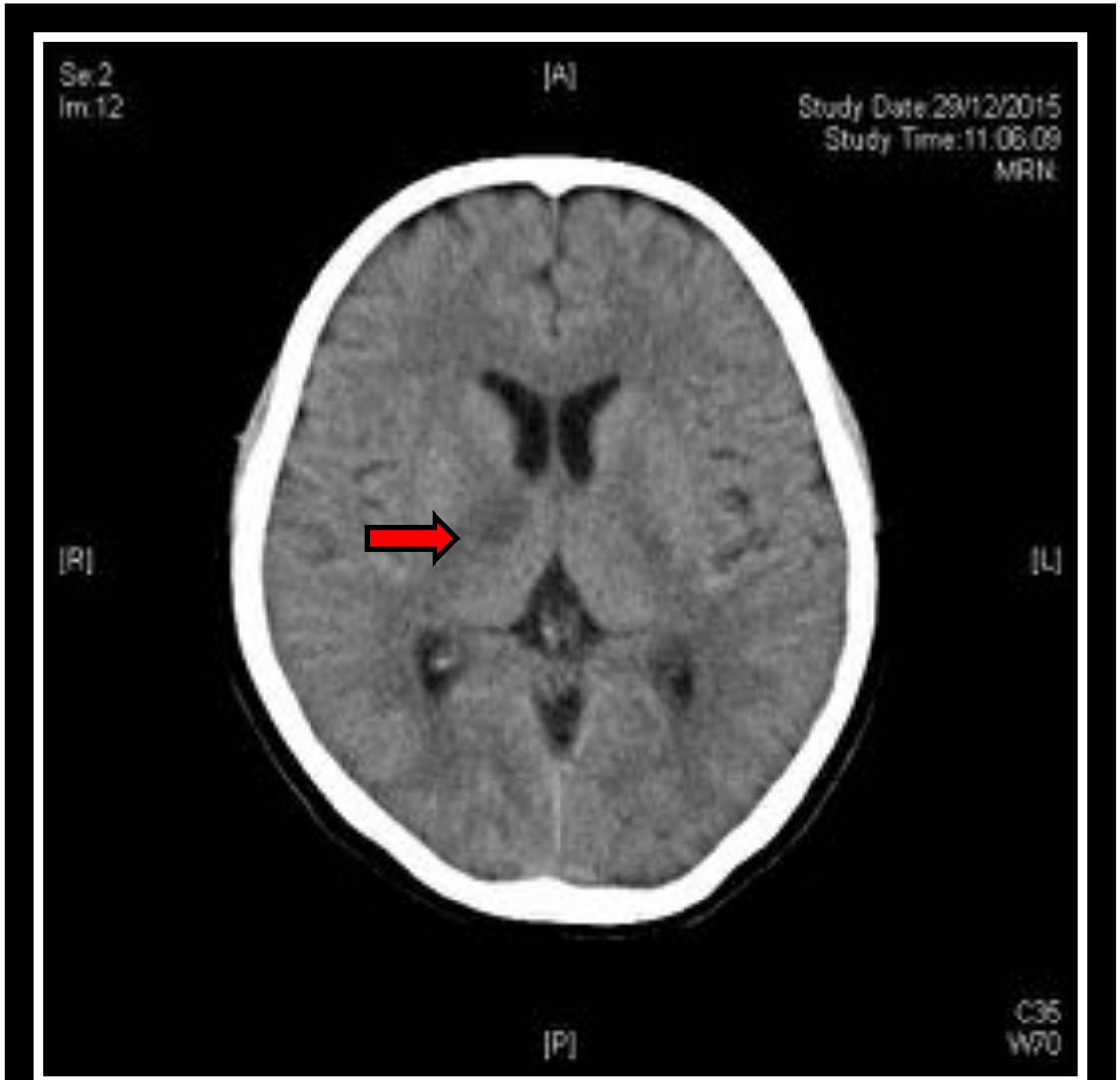
- T2 hyperintense lesions in left corona radiata may be due to **chronic ischemic change or demyelination**. These are not enhanced by contrast. No restricted diffusion is seen to suggestive of acute ischemic change.
- Mild swelling of the right optic nerve with contrast enhancement in the nerve sheath, suggestive of **right optic neuritis**.

This admission

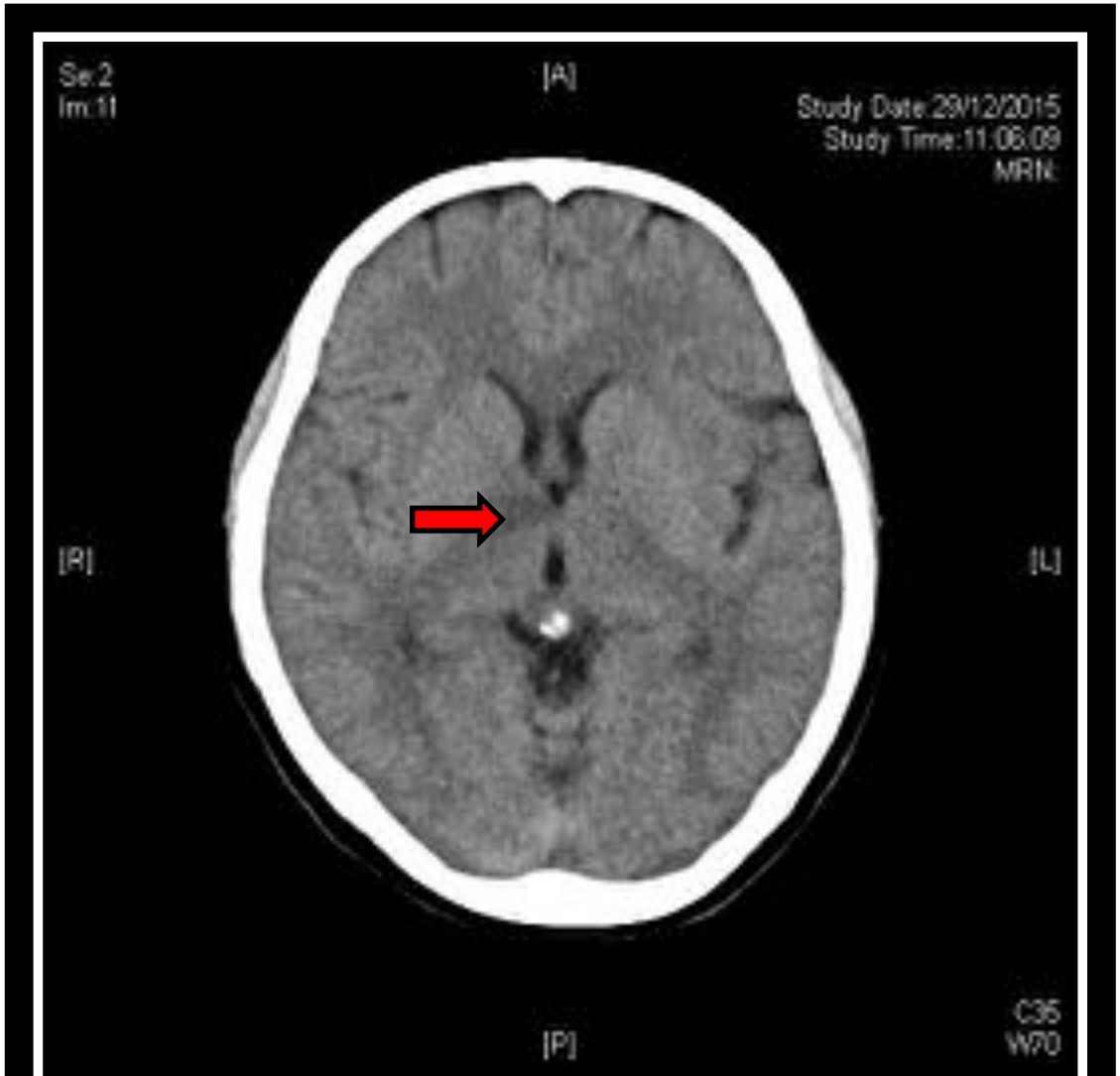
Late December

- Admitted to EYE on 24/12/2015 for recurrent right optic neuritis, decreased vision
- Restarted on Methylprednisolone 250mg Q6H for 3 days
- RAPD on admission, improved on Day 3, but developed right sided headache
- Fever to 38 degrees on Day 4, then left hemiplegia and slurred speech in early morning

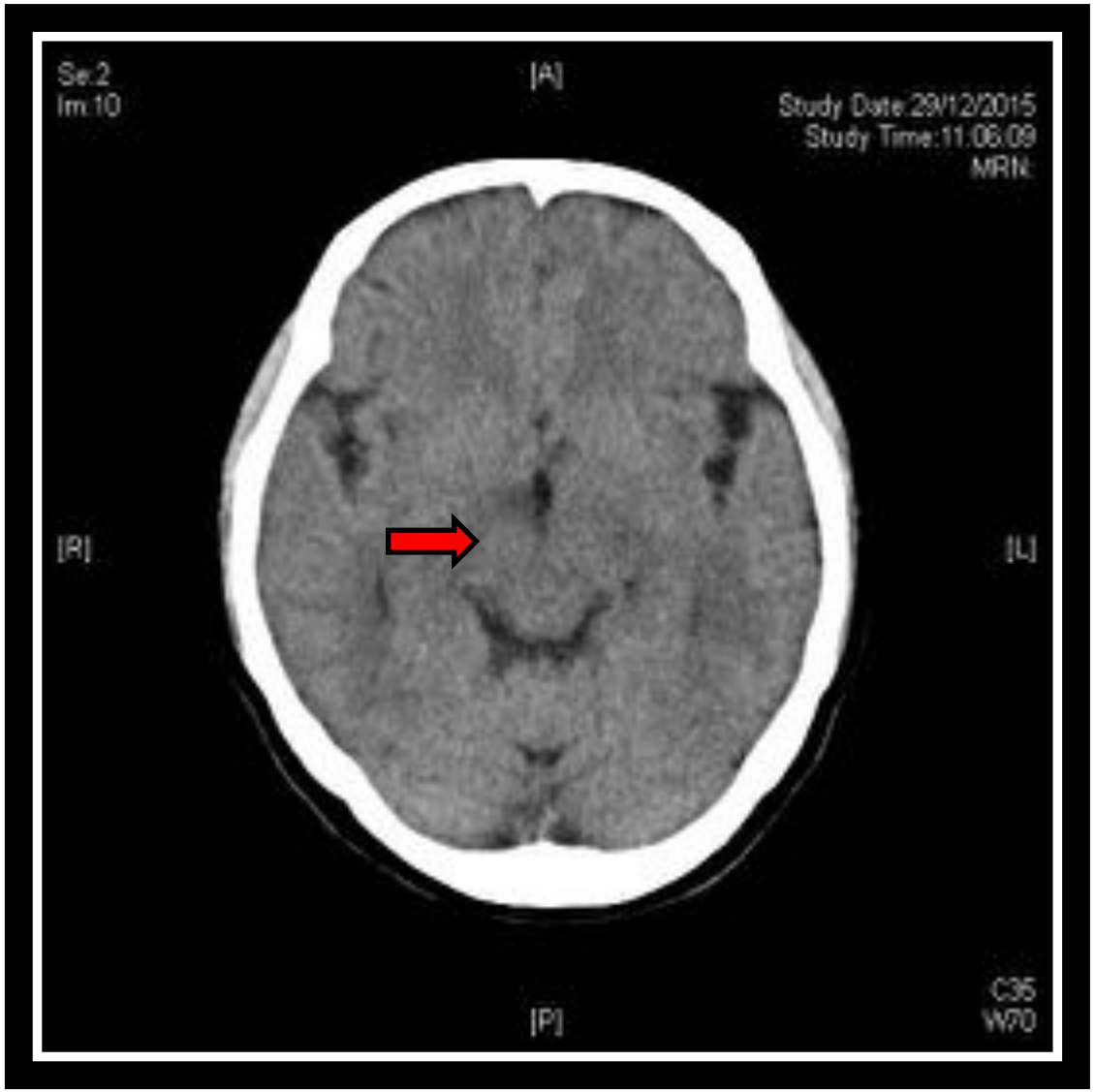
29/12/2016 CT Brain



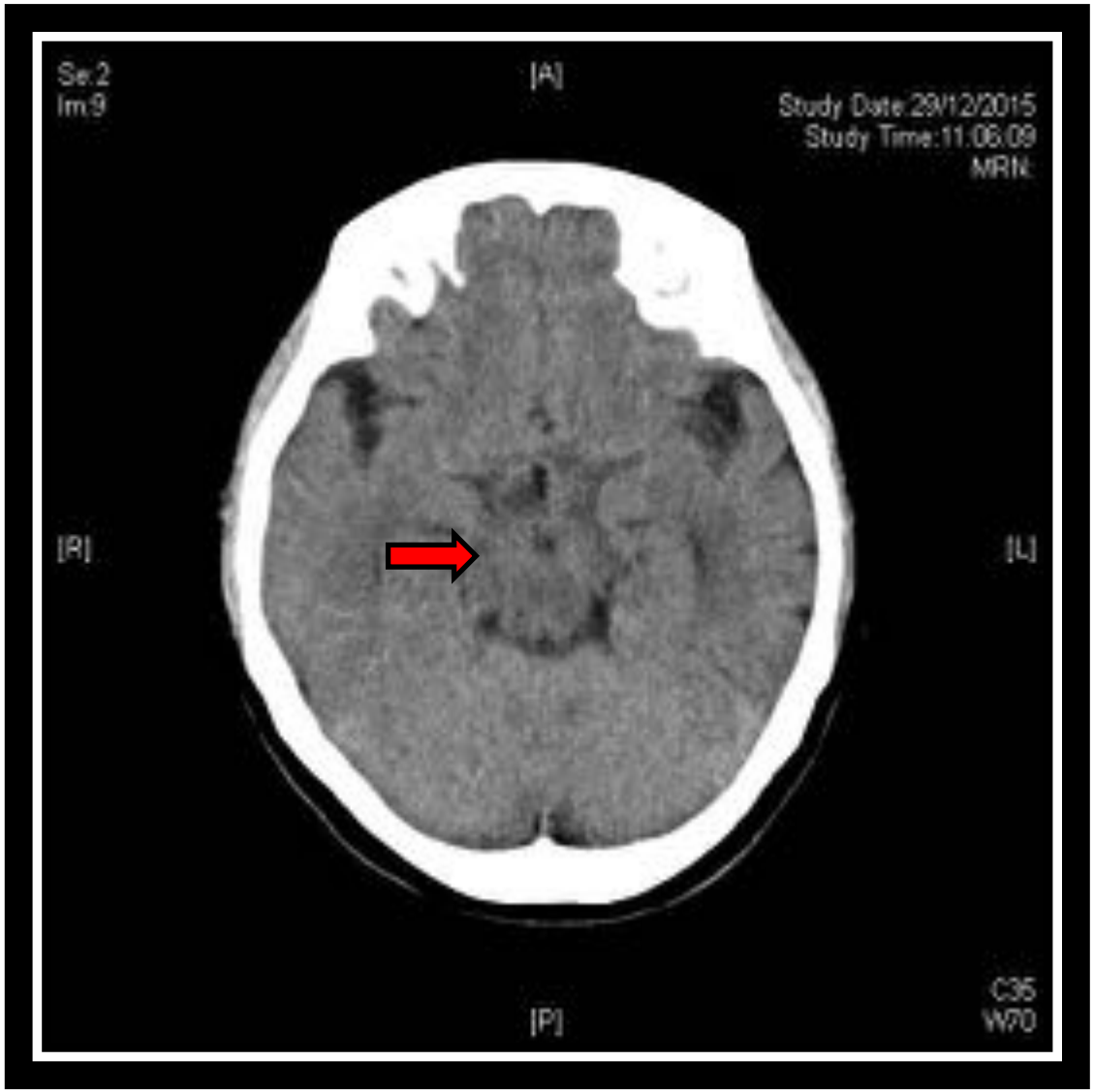
29/12/2016 CT Brain



29/12/2016 CT Brain



29/12/2016 CT Brain



CT Report same Day

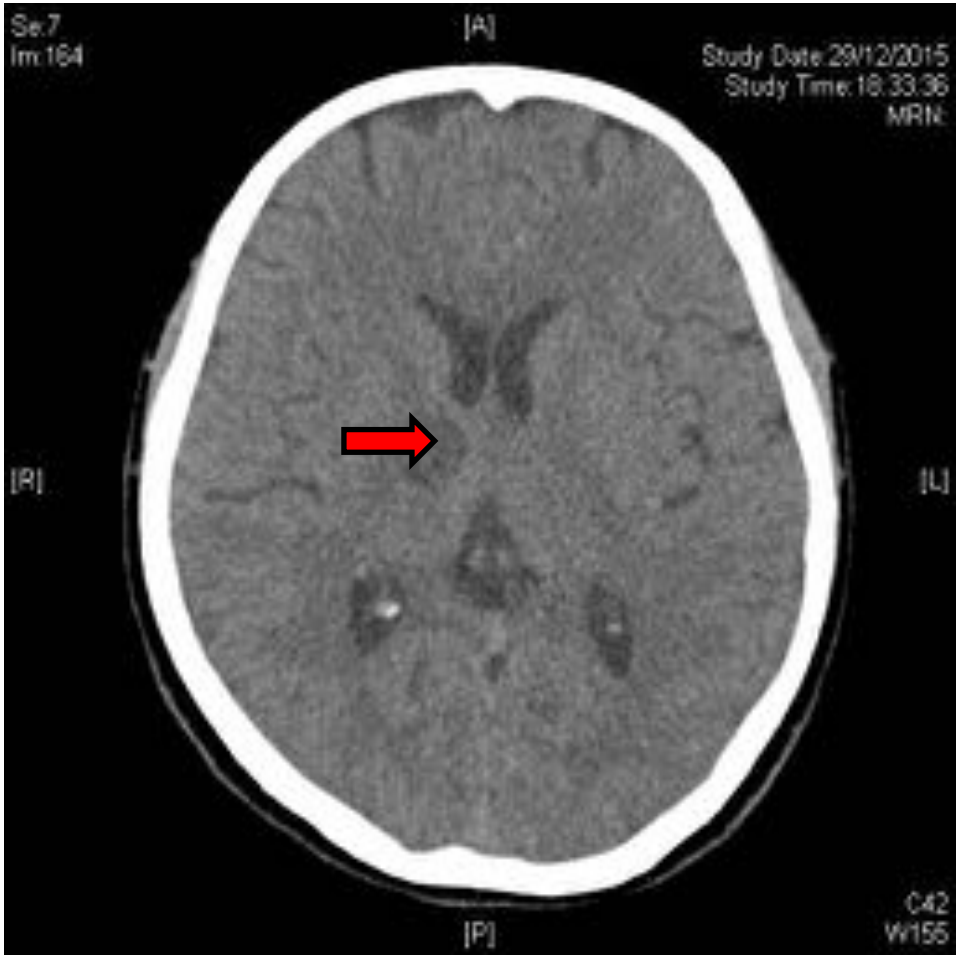
- Small **hypodense infarct** over genu of right internal capsule to thalamus.
- Tiny lacunar infarcts also seen at both external capsules.

- Increased **hyperdensity seen at right pre-pontine cistern**. Not seen in last CTB (done in Nov 2015 in KWH) **suspected Small SAH**.

Neurosurgery consulted for ?SAH

- Suggested CTA→
- CTA done 5 hours after first CT
  - Circle of Willis looked well formed. Dysplastic left vertebral artery, can be congenital.
  - Right PCA supplied by anterior circulation via PCom with dysplastic P1, normal variant.
  - No abnormal stenosis, aneurysm or vascular malformation seen.
  - Suspicious SAH static

Contrasted CT



Case Presentation

- Investigations result - CBC

	29/12	30/12	Reference Range	Units
WBC	17.0	15.1	3.70 – 9.20	X 10^9/L
RBC	4.64	5.24	4.30 – 5.90	X 10^{12}/L
HGB	13.8	15.7	13.40 – 17.10	g/dL
MCV	92.0	91.0	82.0 – 97.0	Fl
PLT	209	223	145 – 370	X 10^9/L
Neutrophil	14.2	12.7	1.7 – 5.8	X 10^9/L
Lymphocyte	1.0	0.9	1.0 – 3.1	X 10^9/L
Monocyte	1.8	1.4	0.0 – 0.5	X 10^9/L

Case Presentation

- Investigations result – LRFT

	29/12	30/12	Reference Range	Units
Urea	4.7	3.8	2.4 – 6.5	mmol/L
Creatinine	73	77	55 – 103	mmol/L
Sodium	139	147	136 – 144	mmol/L
Potassium	3.2	3.5	3.3 – 4.6	mmol/L
Calcium	2.10		2.07 – 2.37	mmol/L
Phosphate	1.10		0.83 – 1.43	mmol/L
Bilirubin	17	20	1.7 – 5.8	umol/L
ALP	58	78	1.0 – 3.1	U/L
ALT	583	400	< 46	U/L
Albumin	32	32	37 – 47	U/L
Globulin	34	41	25 - 39	U/L

HbsAg negative

Anti-HAV IgM negative

Anti-HCV negative

Lumbar puncture 30/12/2016

- Opening Pressure: 14cm Water
- Slight turbid CSF

Appearance :-
Slightly Blood-stained

Cell Count :-

Red blood cells	: Greater than	10,000	/cubic mm
White blood cells	:	540	/cubic mm
Polymorphs	:	60	%
Lymphocyte	:	40	%

Smear :-
CSF Gram Smear : No organism seen

Bacterial Antigen :

Streptococcus Group B :	Negative
Haemophilus influenzae type B :	Negative
Streptococcus pneumoniae :	Negative
N. meningitidis type B/E.coli K1 :	Negative
N. meningitidis type ACYW135 :	Negative

Cryptococcal antigen
Quantity insufficient

Negative staining
No Cryptococcus seen

CSF Culture :-

No growth obtained after 2 days incubation

Random Glucose = 6.4mmol/L

CSF glucose	1.9 L		2.2 - 3.9	mmol/L #
CSF protein	2.89 H		0.15 - 0.45	g/L #

Taken over to ICU

Further examination in ICU

- Several erythematous nodular subcutaneous lesions on legs
- Suggestive of erythema nodosum

Problems so far:

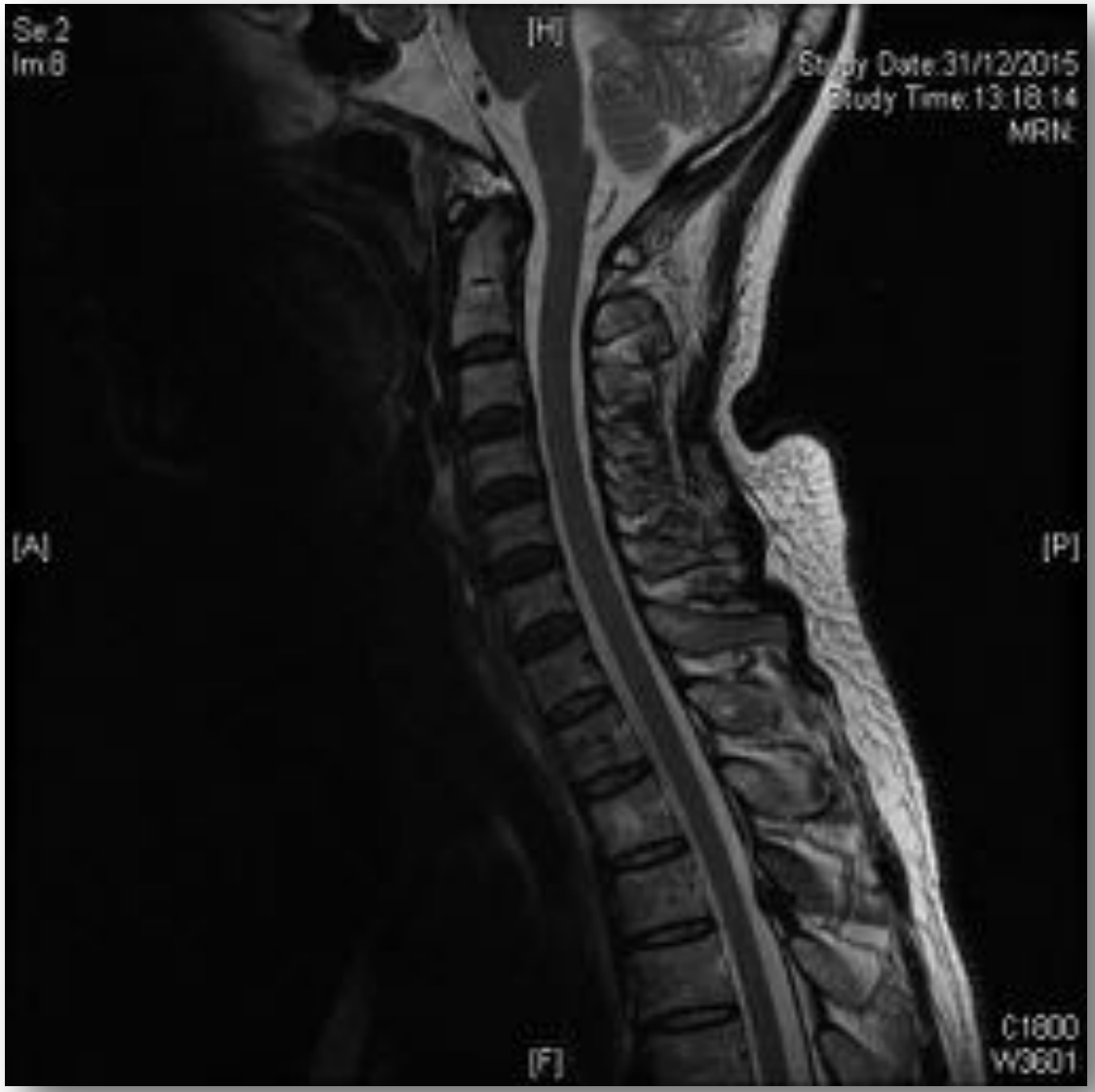
- Deranged Liver function (maybe related to gabapentin, diclofenac)
- Meningitis (Polymorphs-Lymphocyte equivocal, LOW glucose, HIGH protein)
- Multiple sclerosis/Neuromyelitis Optica
- Right thalamic infarct
- Suspected SAH

31/12/2015 in ICU

- Tachycardia, BP stable, Fever to 39 degrees
- GCS E3V1M6
- Urine output 30mL/hour
- Right RAPD, neck soft
- No vomiting so far

- EEG - no epileptiform activity seen, study suggestive of mild to moderate cerebral dysfunction
- Ultrasound abdomen: No focal lesion
- MRI Brain and spine done

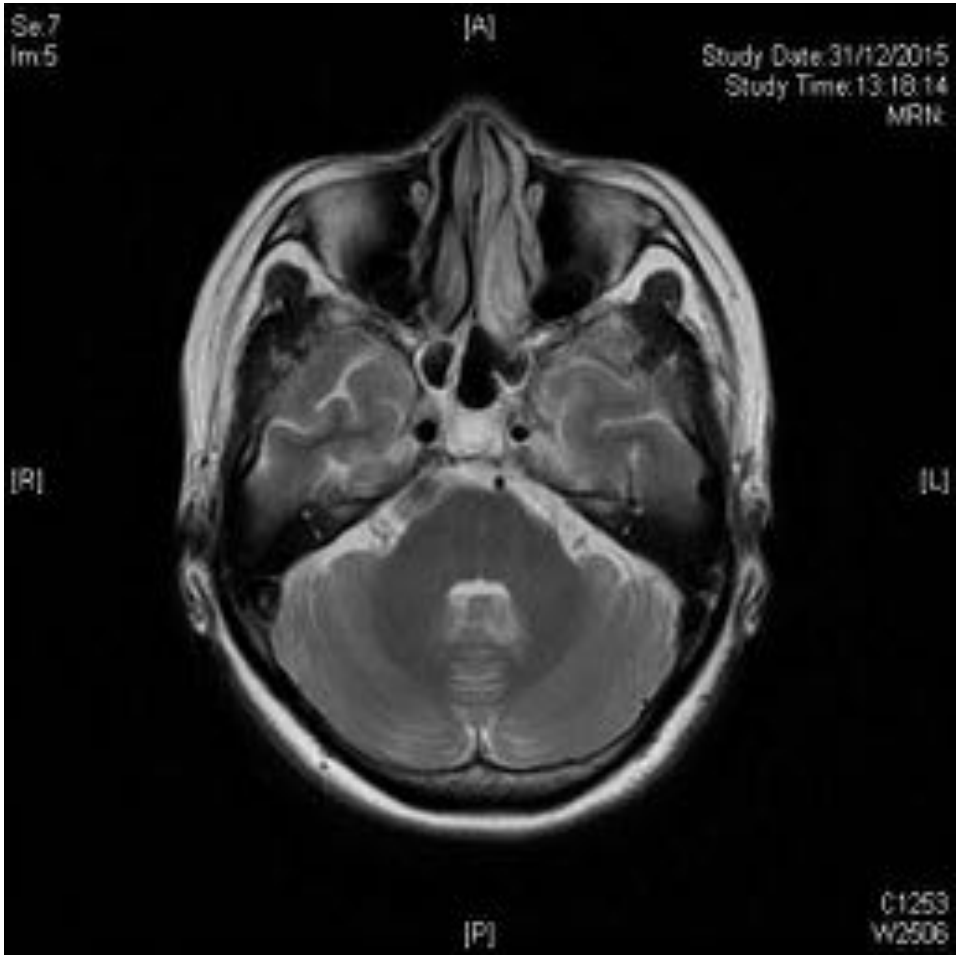
MRI Spine 30/12/2016



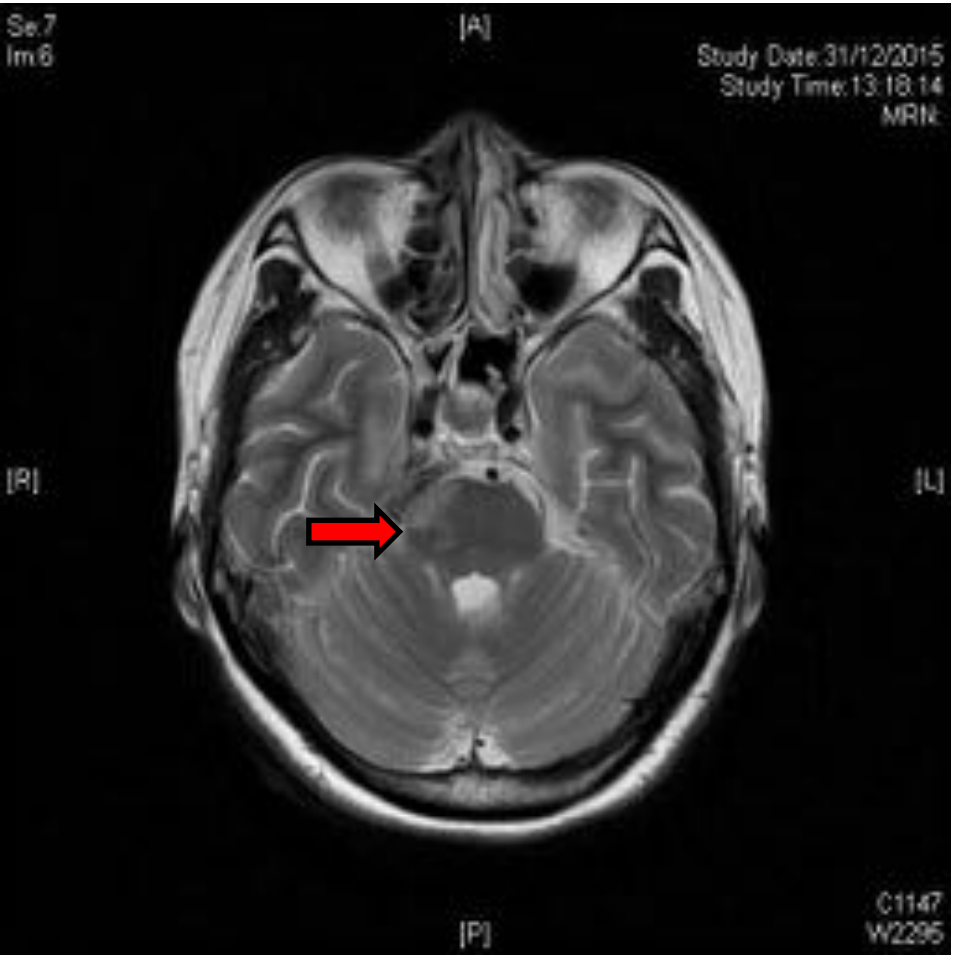
MRI Spine 30/12/2016

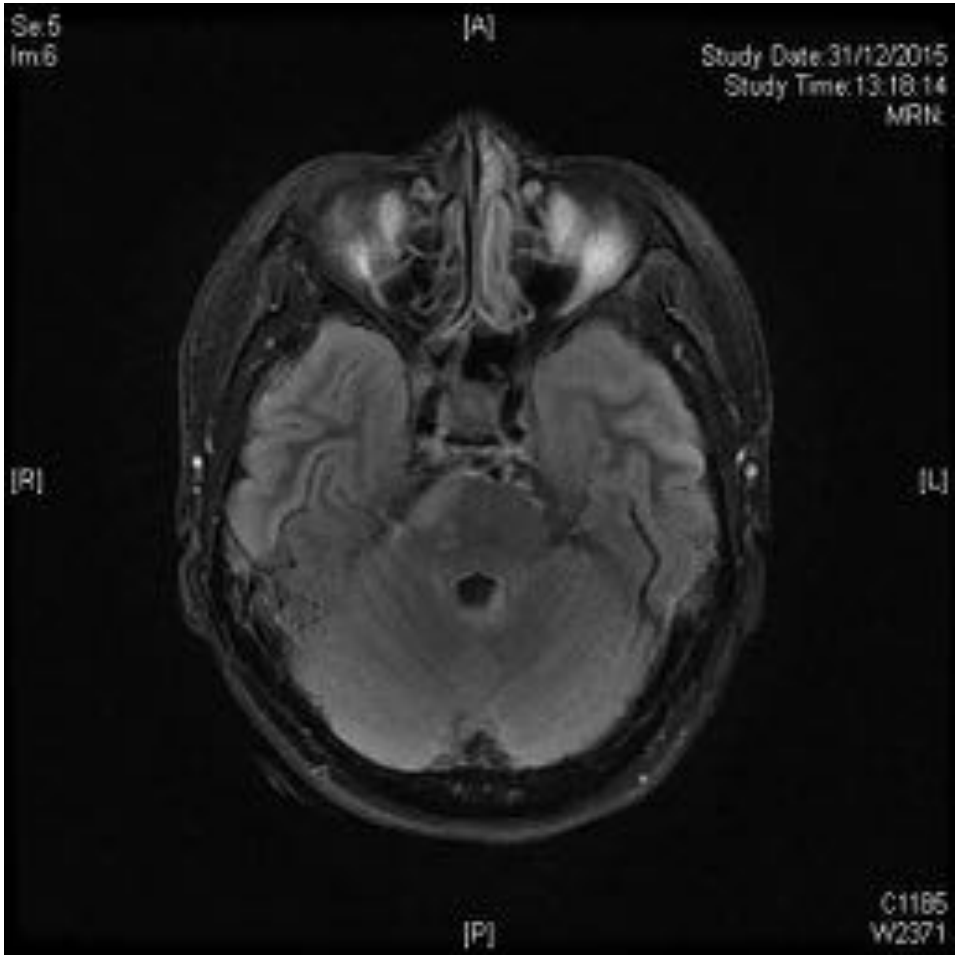
- No cervical cord lesion seen in supplementary examination of the cervical spine and cannot explain changes near skull base

MRI Brain 31/12/2015

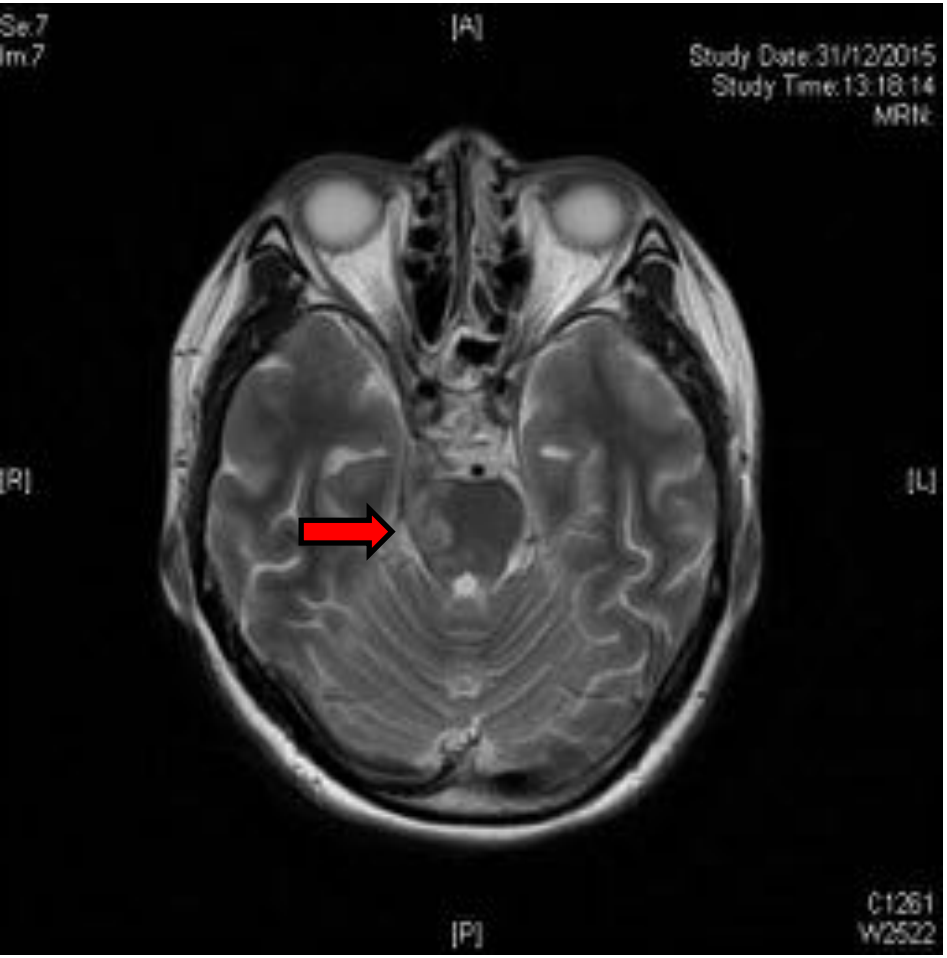


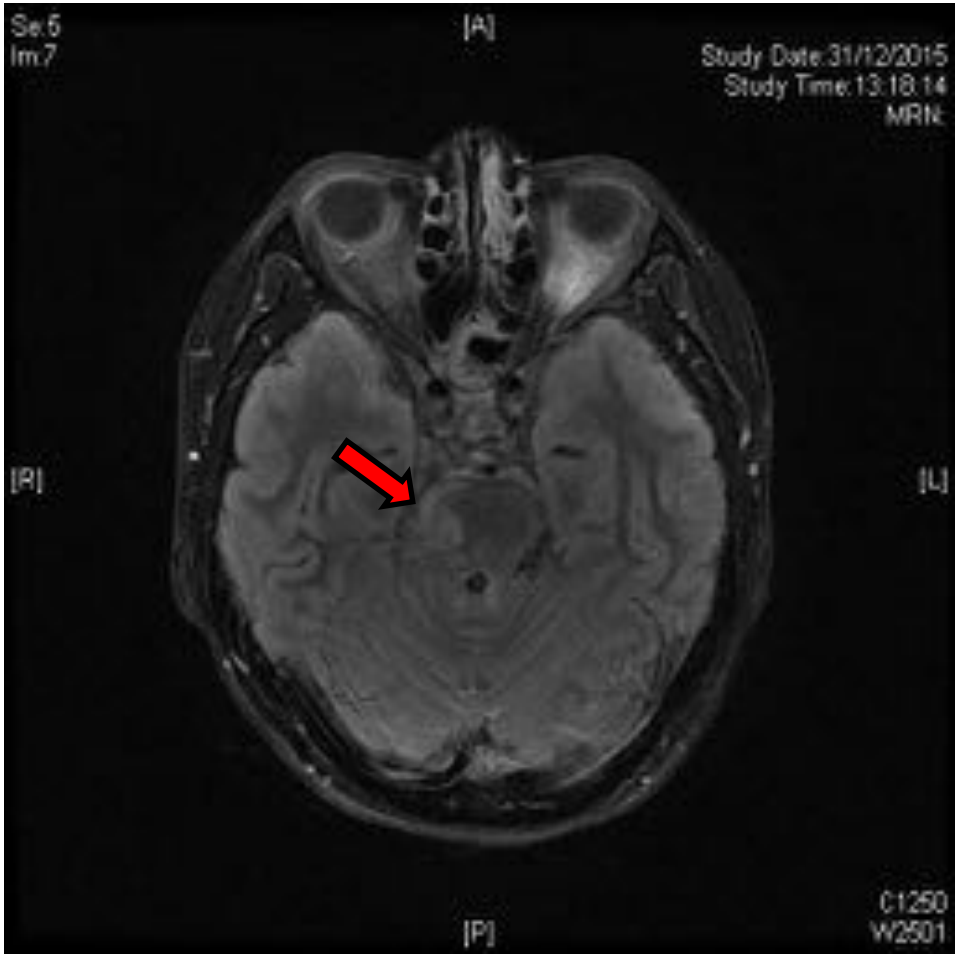
MRI Brain 31/12/2015



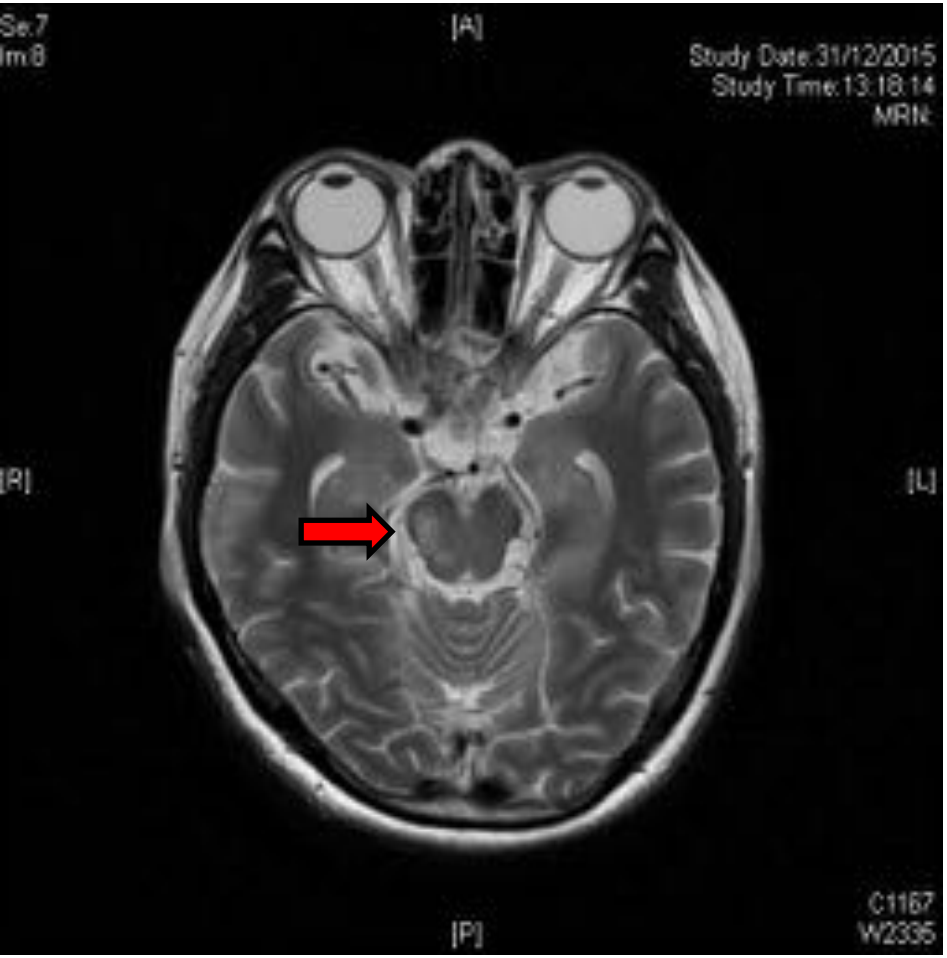


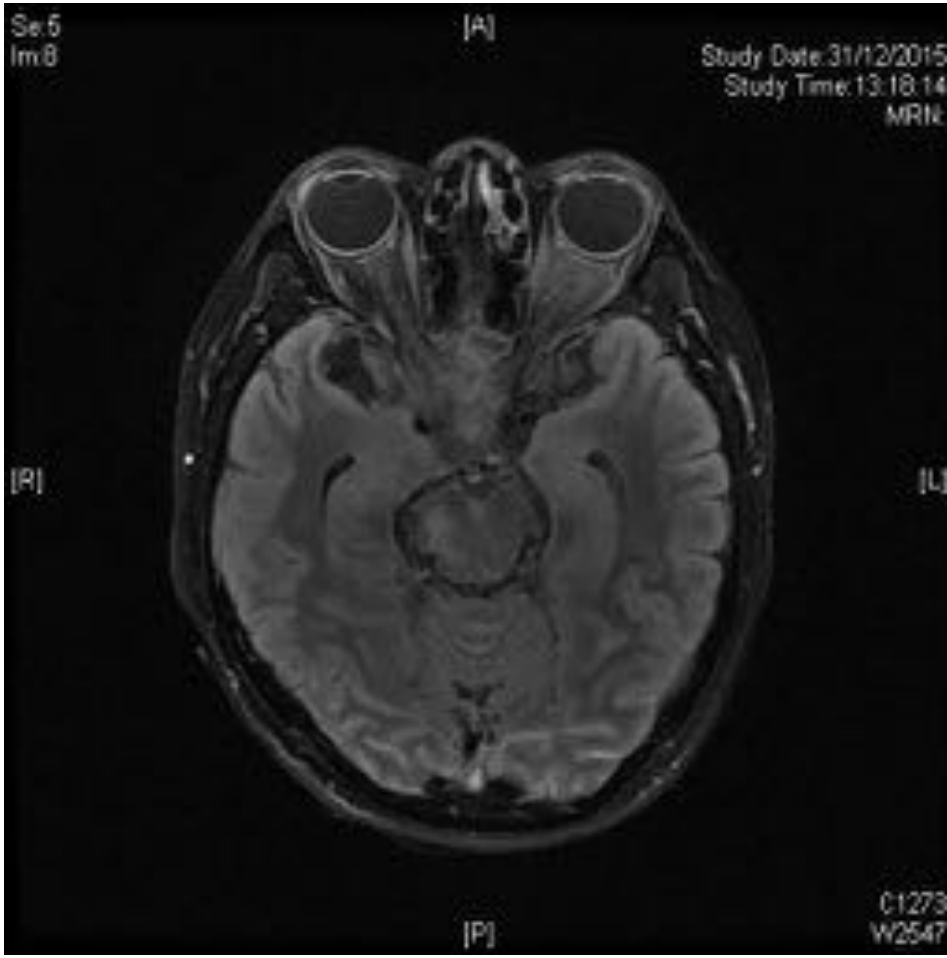
MRI Brain 31/12/2015



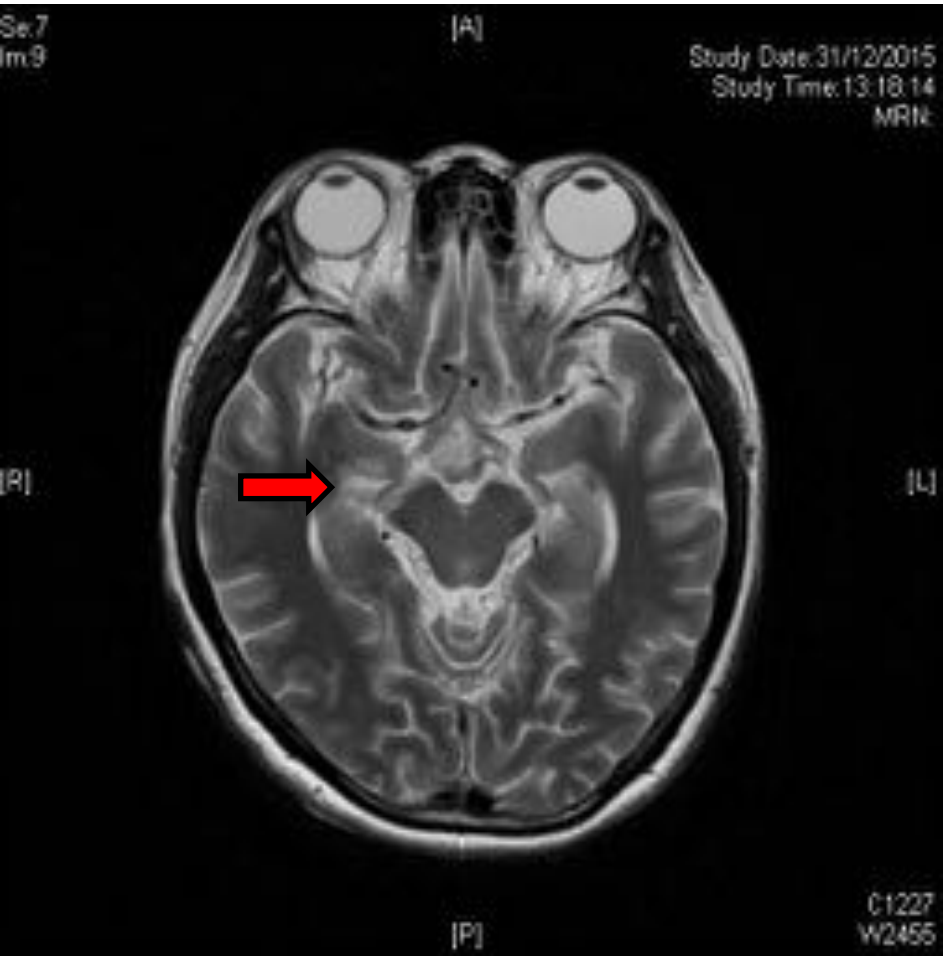


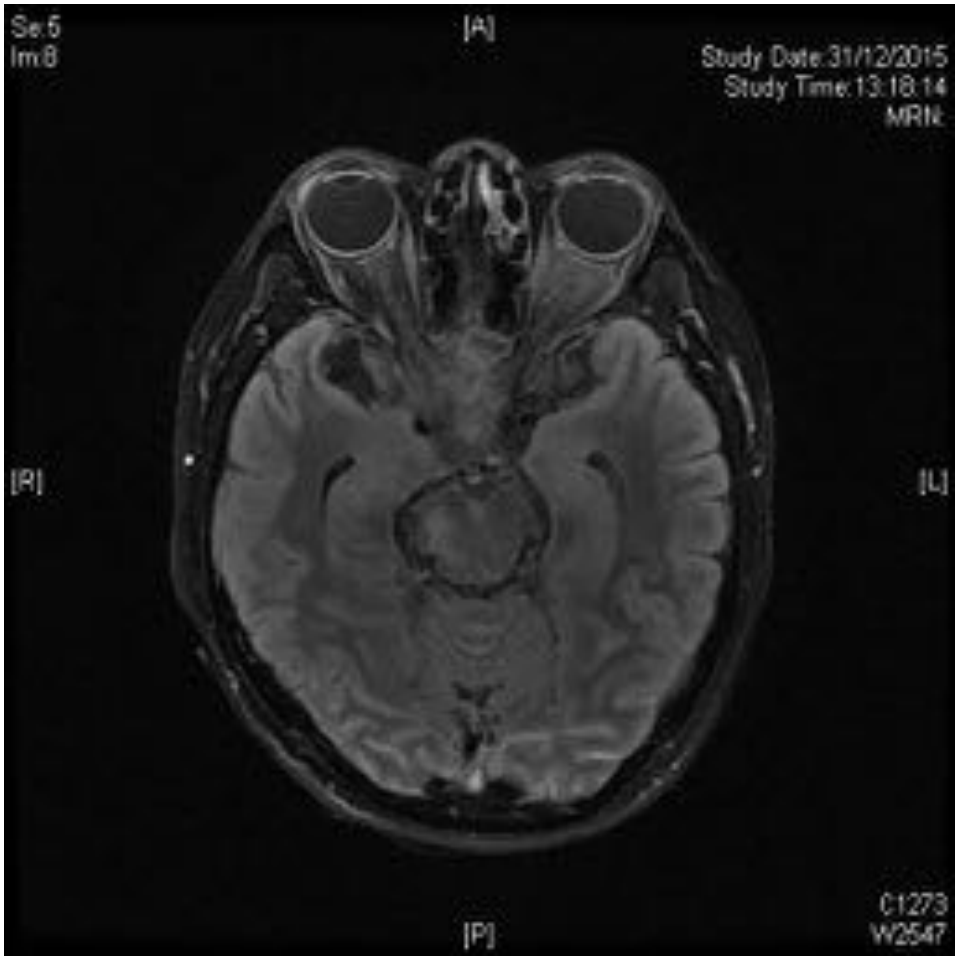
MRI Brain 31/12/2015



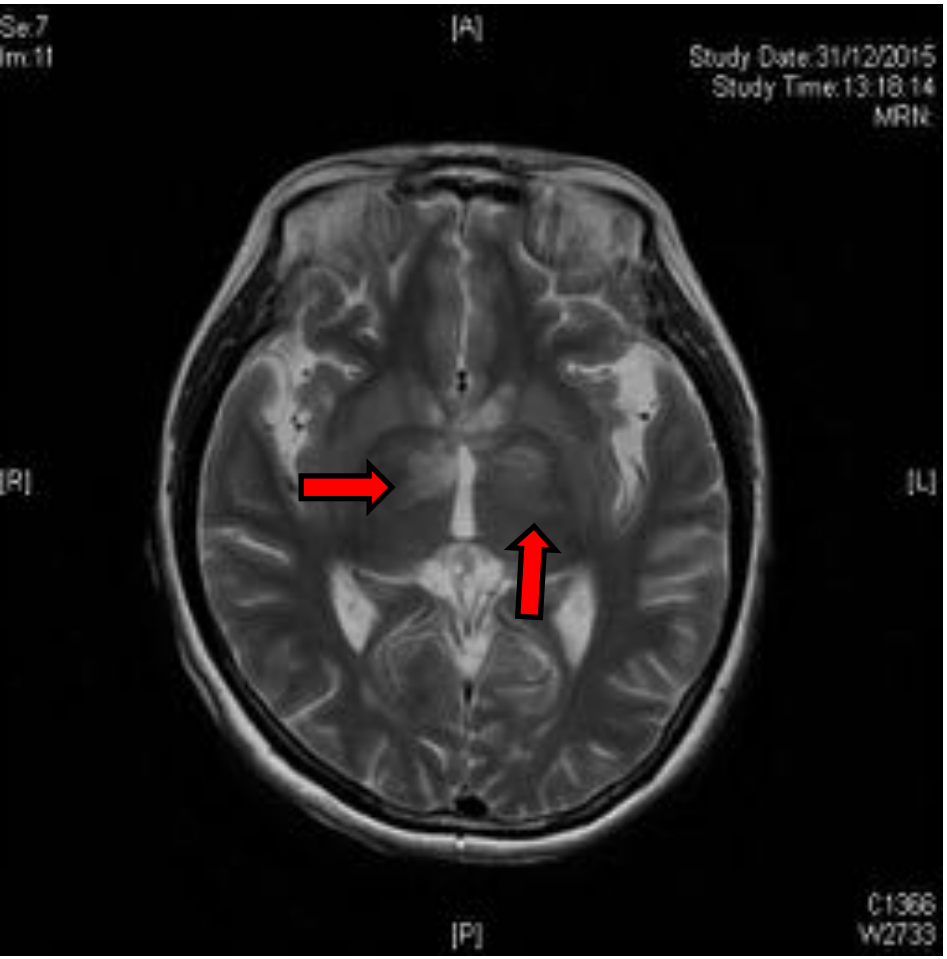


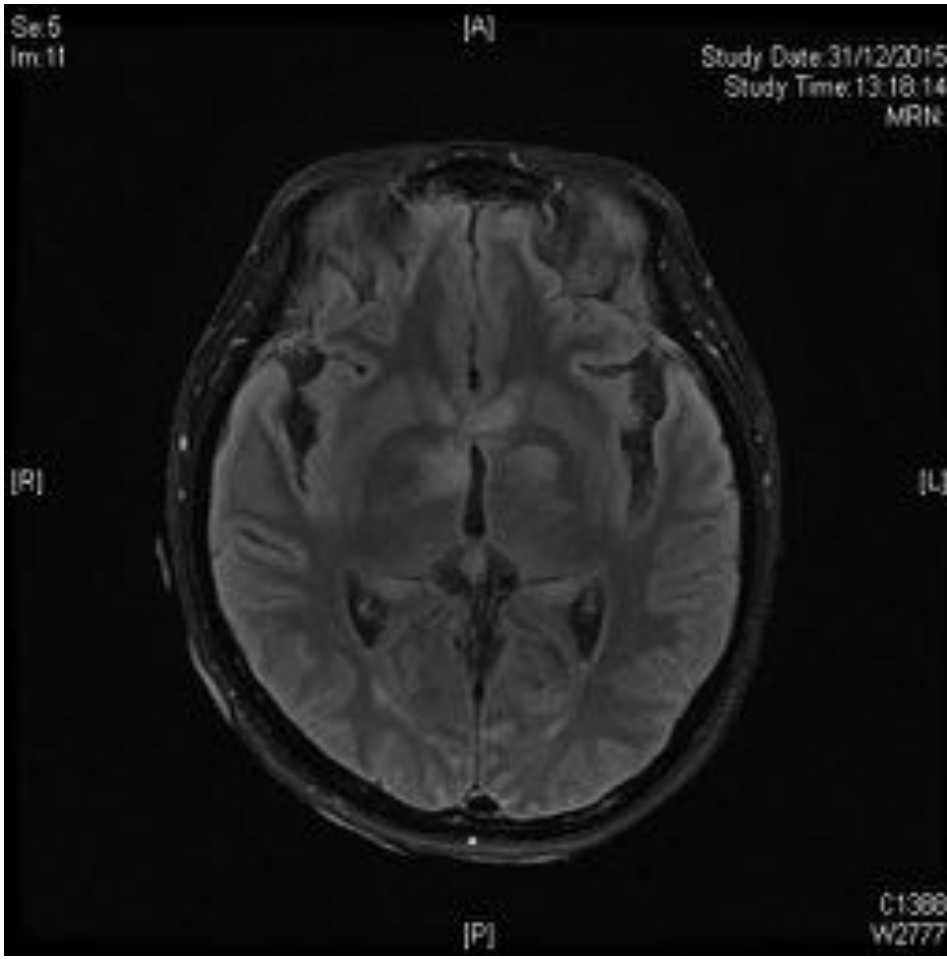
MRI Brain 31/12/2015



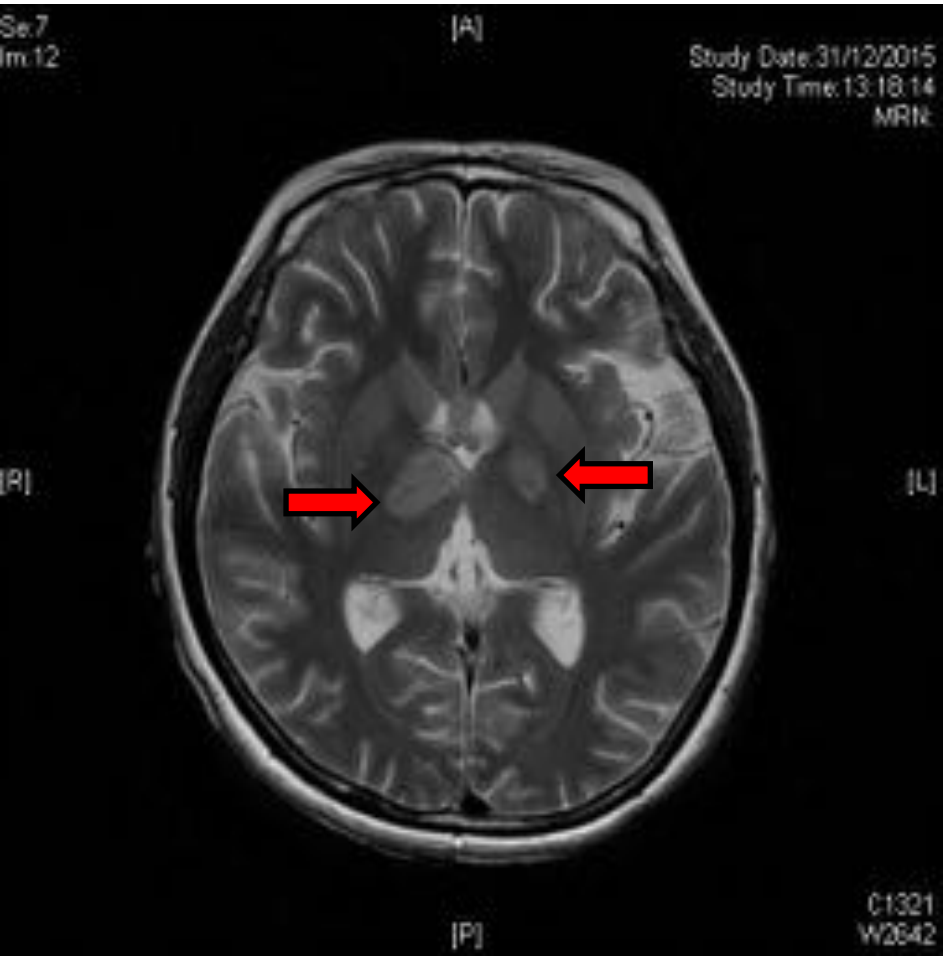


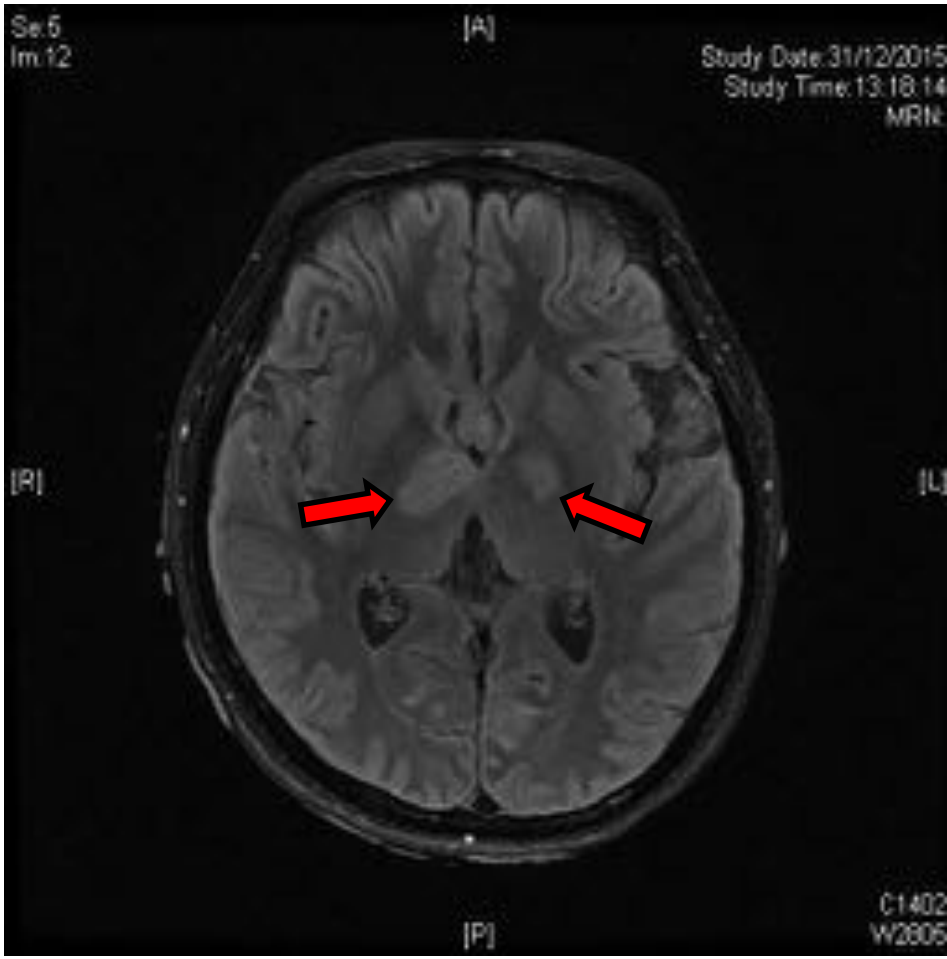
MRI Brain 31/12/2015





MRI Brain 31/12/2015





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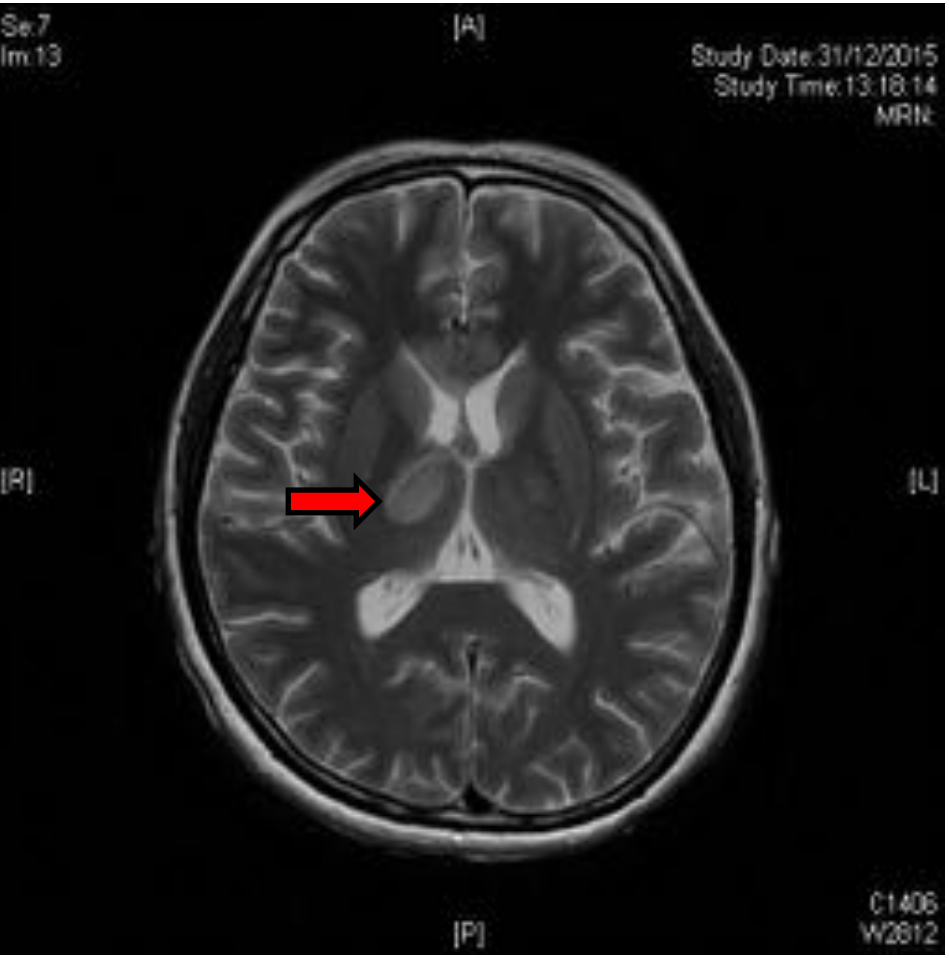
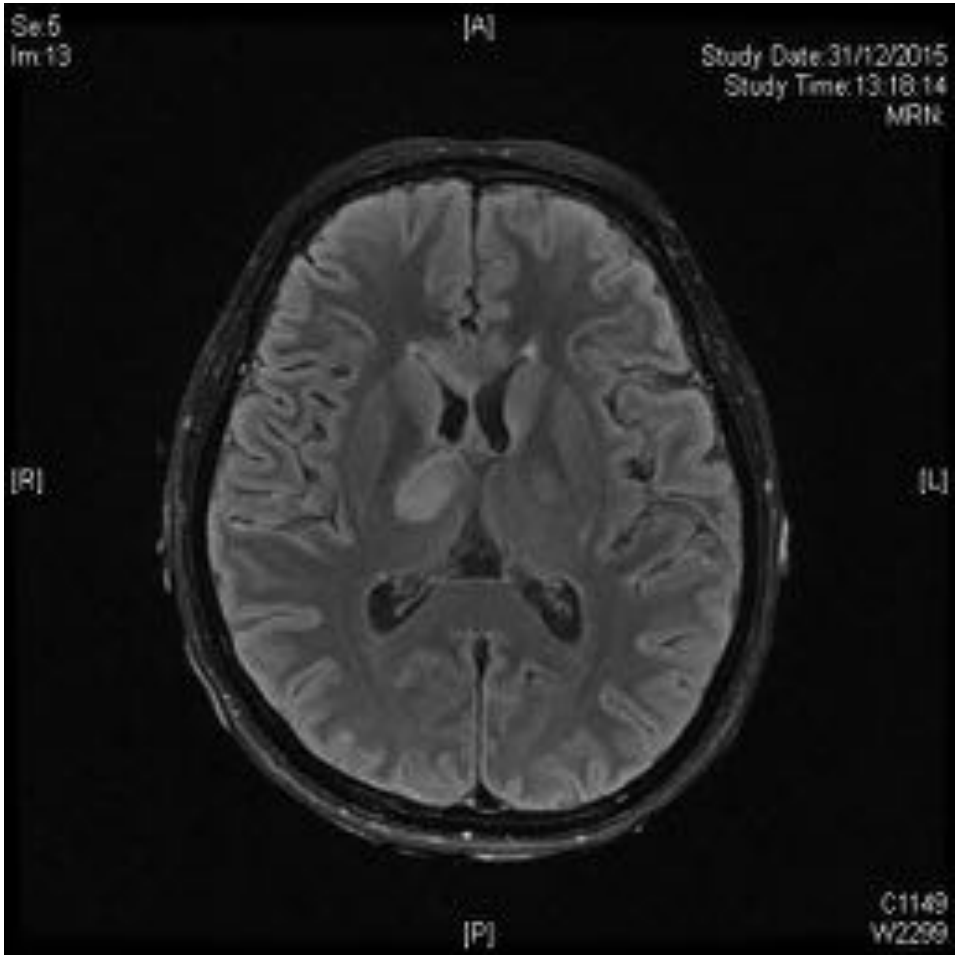
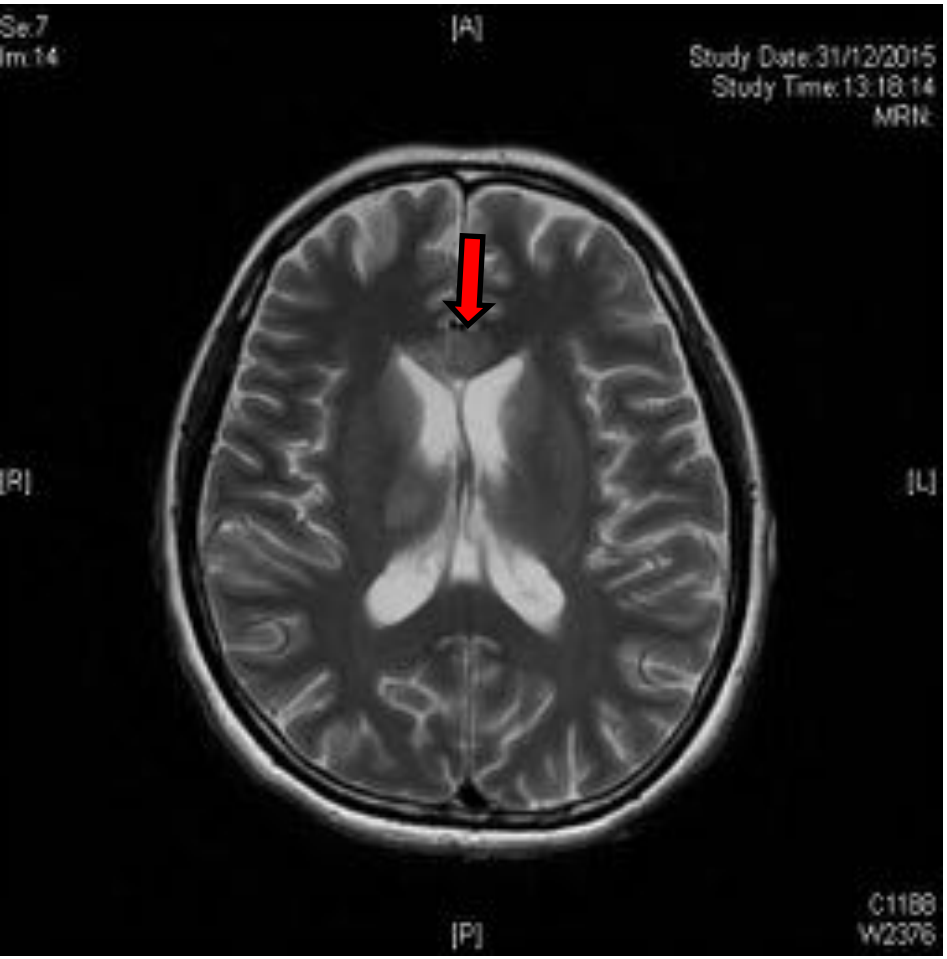
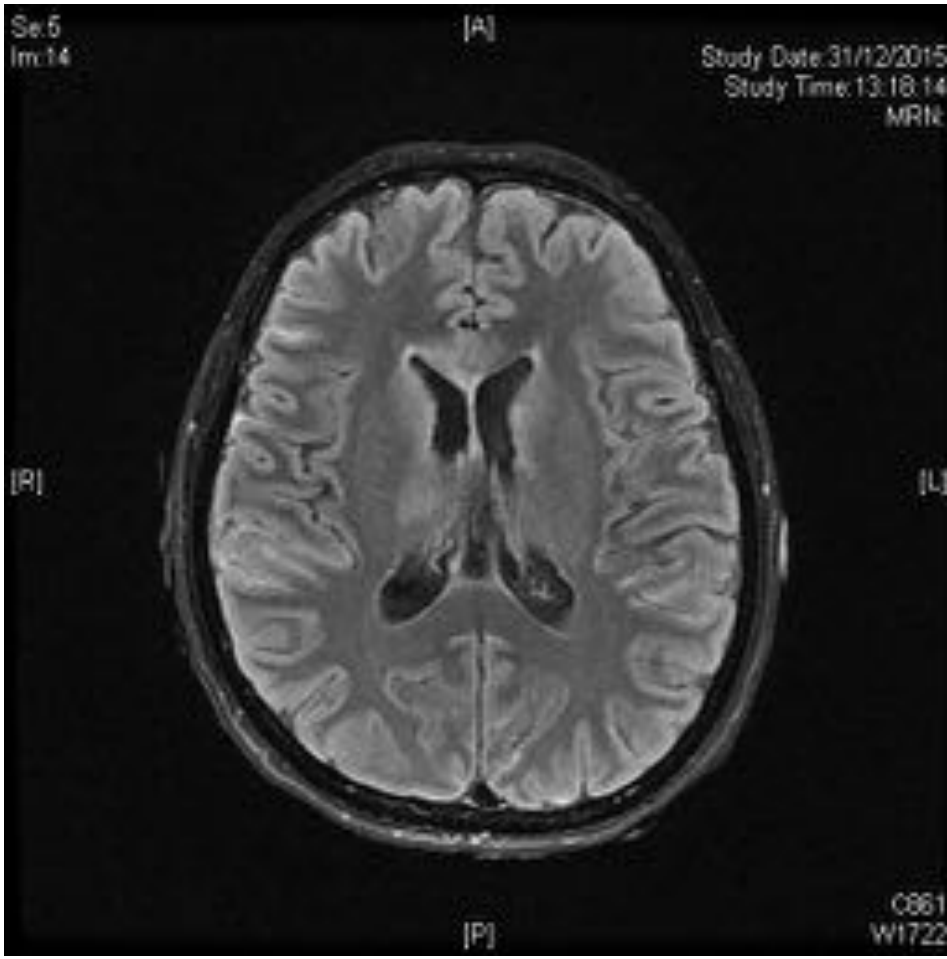


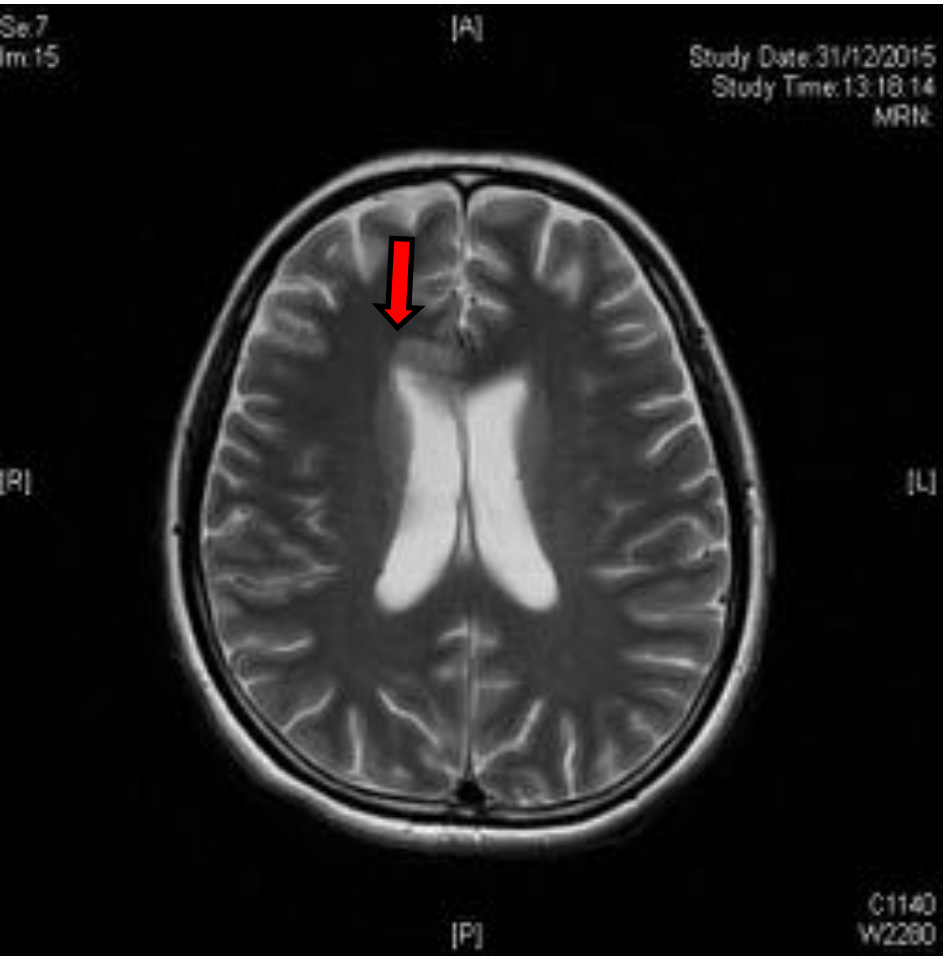


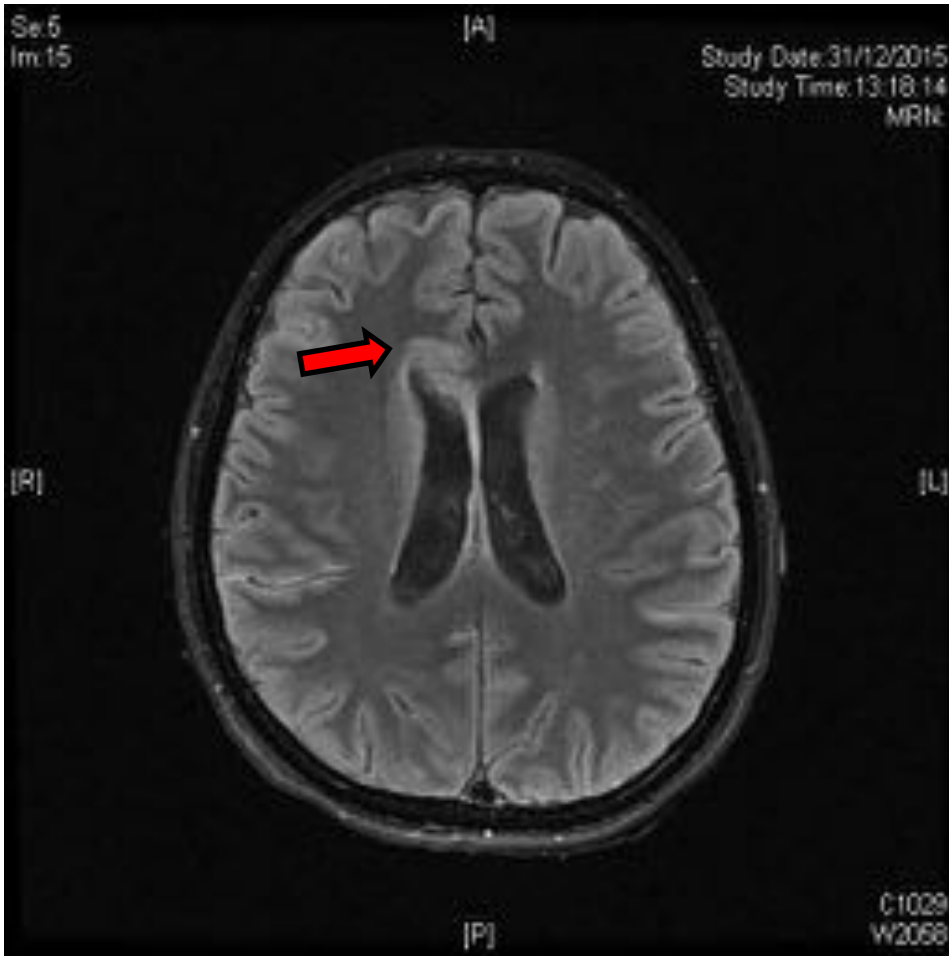
MRI Brain 31/12/2015





MRI Brain 31/12/2015





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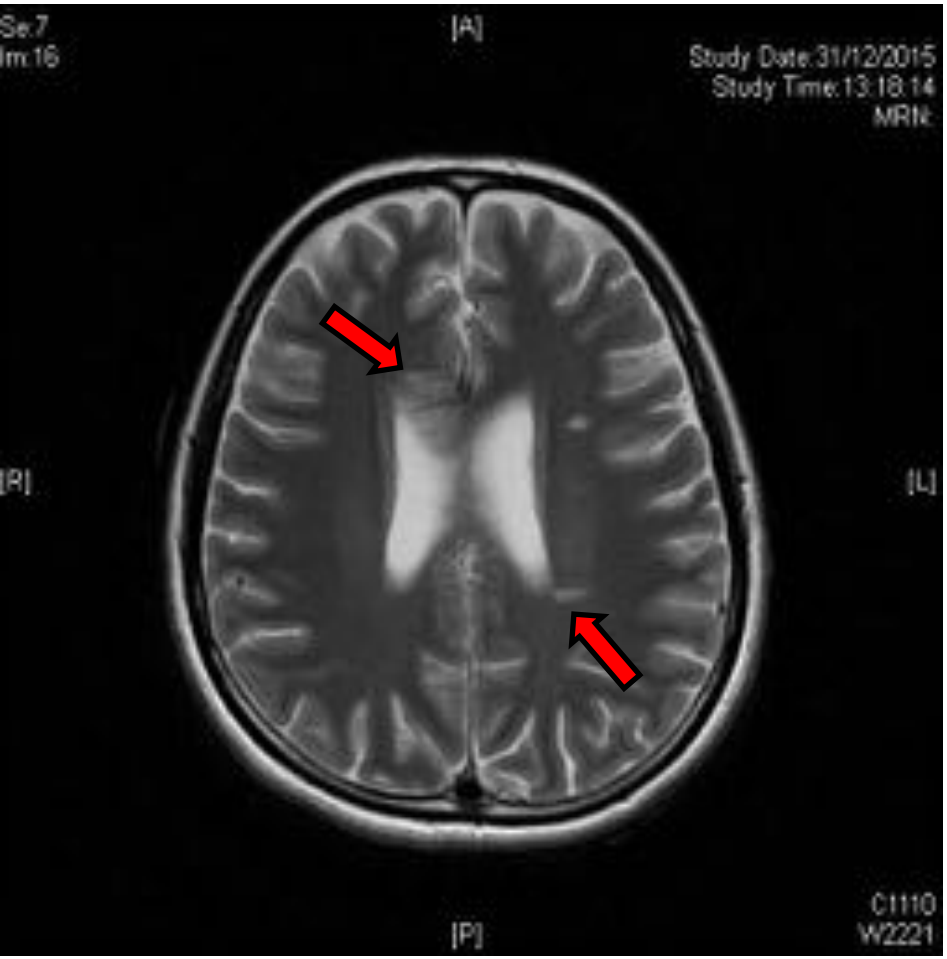
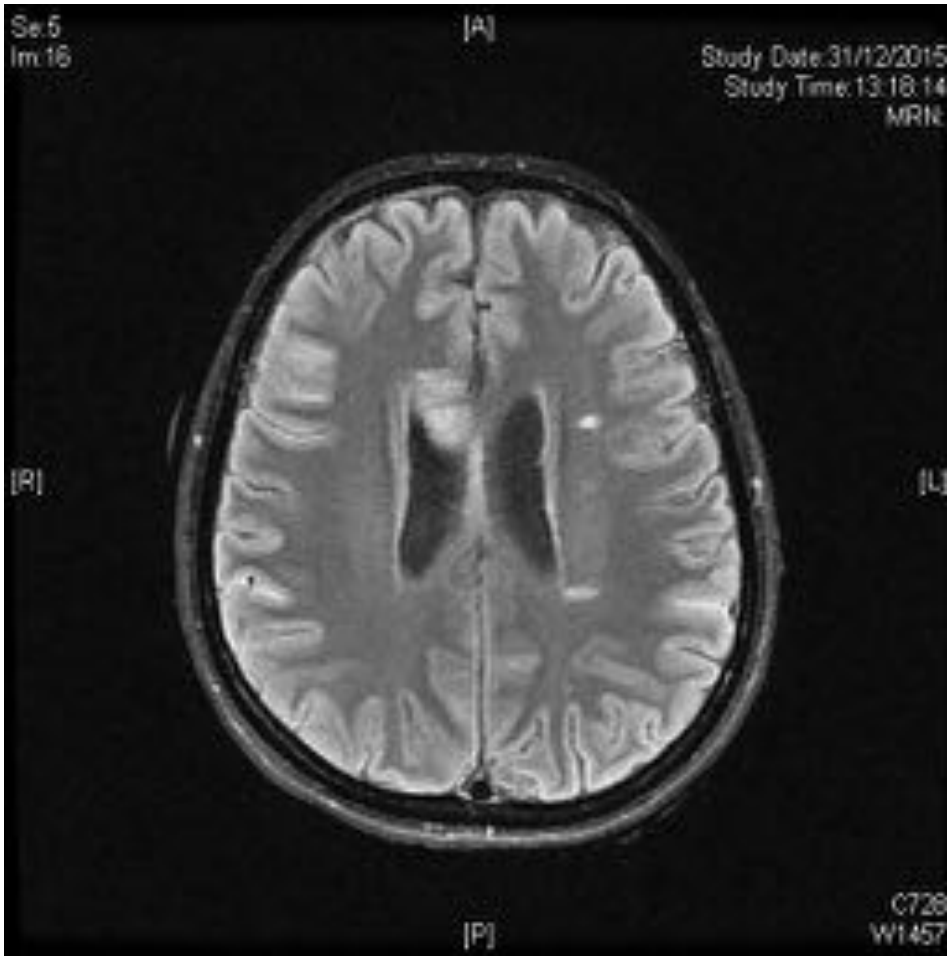




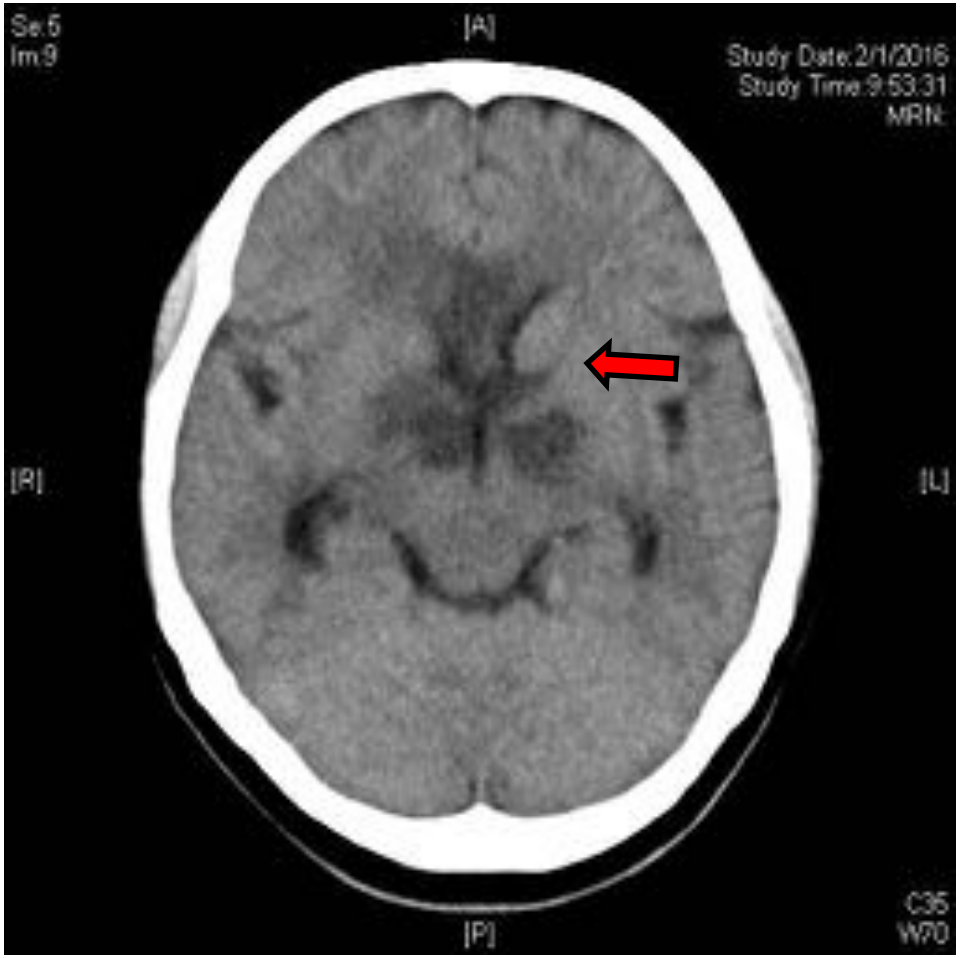
MRI Brain 31/12/2015

- T2 hyperintense lesions found in bilateral thalamic regions, extends toward the third ventricle, the right midbrain-pons, peri-aqueductal region and optic chiasma.
- T2 hyperintense lesions also seen in left corona radiata (elongated lesions perpendicular to the ventricle), corpus callosum (crossing midline) and right medial temporal lobe.
- Subtle enhancement seen in region of right 5th cranial nerve, around optic chiasma and around right side of pons. The lesion in corpus callosum also shows mild enhancement. Otherwise the other lesions are not enhancing and no suggestion of brain abscess seen.

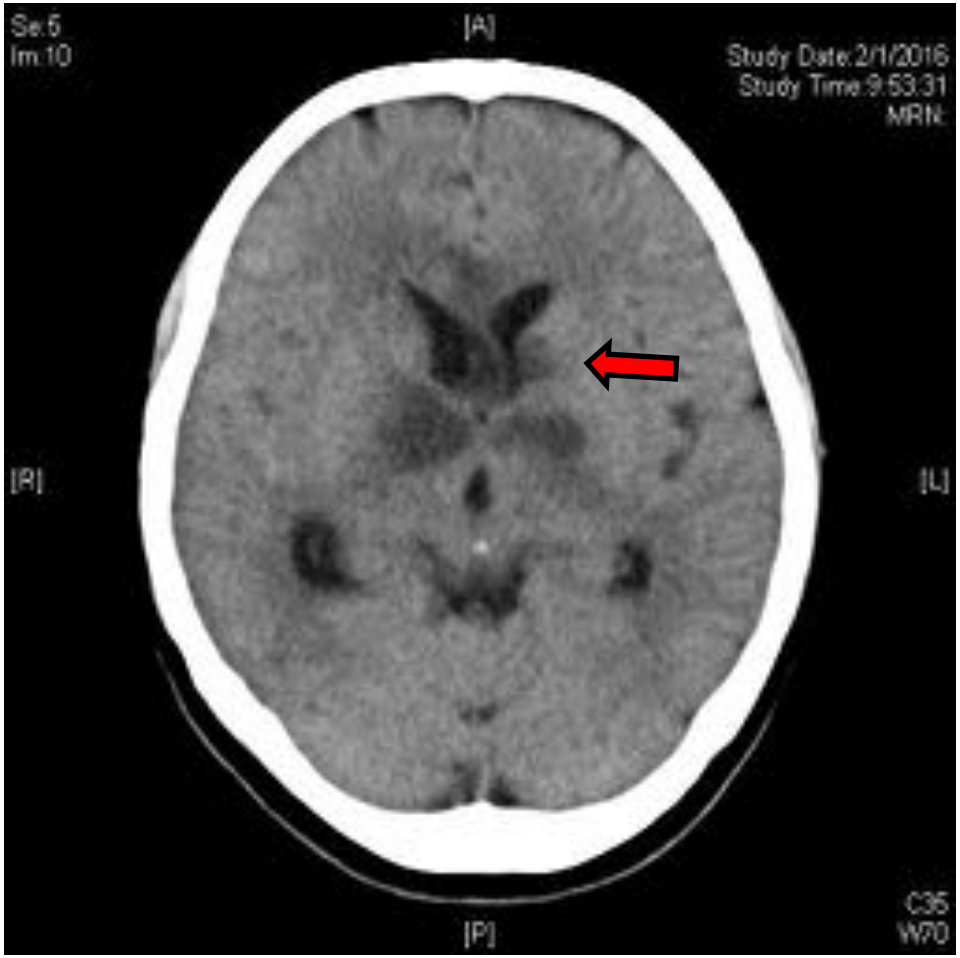
Subsequent Progress

Date	
31/12/2015	• Discussed with Microbiologist: Started on Levofloxacin 500mg Q24H + Isoniazid 150mg Daily for 2 days then 300mg Daily, Pyrazinamide 1.5g Daily, Monitor Liver function closely • Check Anti-HIV and Japanese encephalitis antibody • Neurosurgery: No active intervention • IVF change to D5 as rising Sodium level
1/1/2016	• GCS E2V1M5, No movement on Left limbs
2/1/2016	• GCS E1V1M5, Remained in low grade fever • Decided for intubation • Urgent Repeat CT brain

CT brain 02/01/2016



CT brain 02/01/2016



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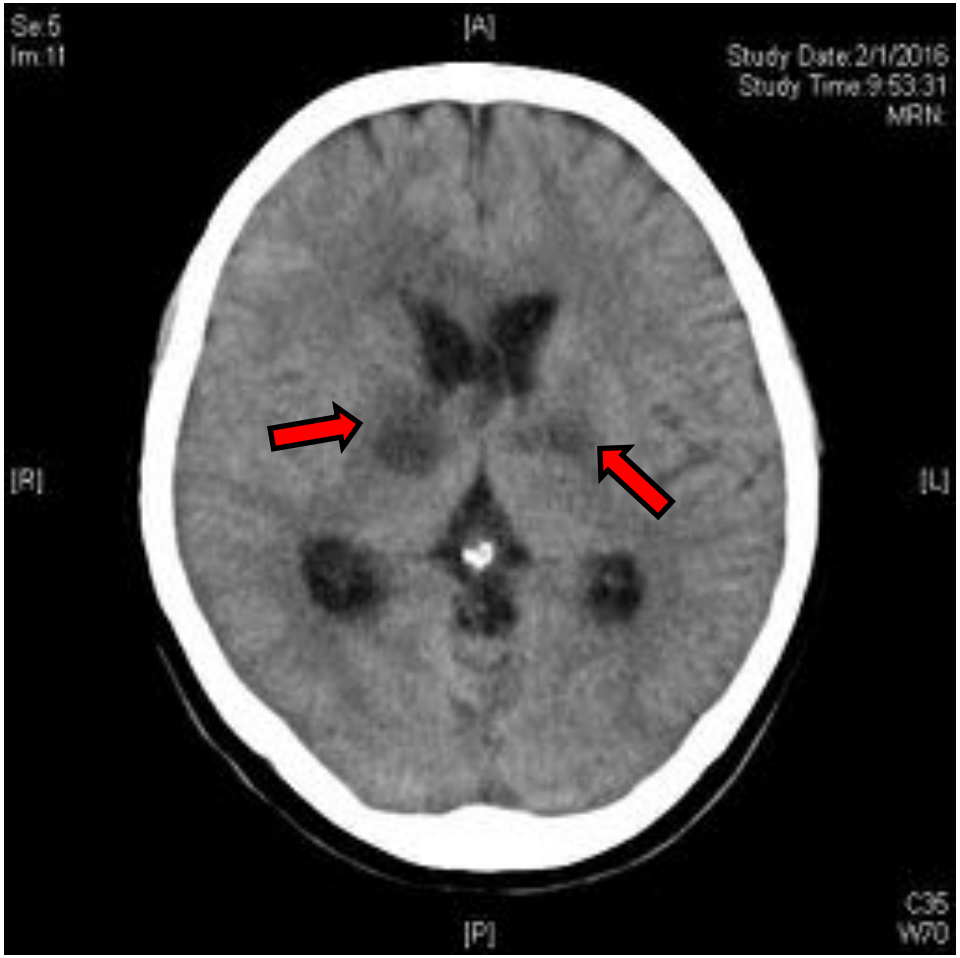
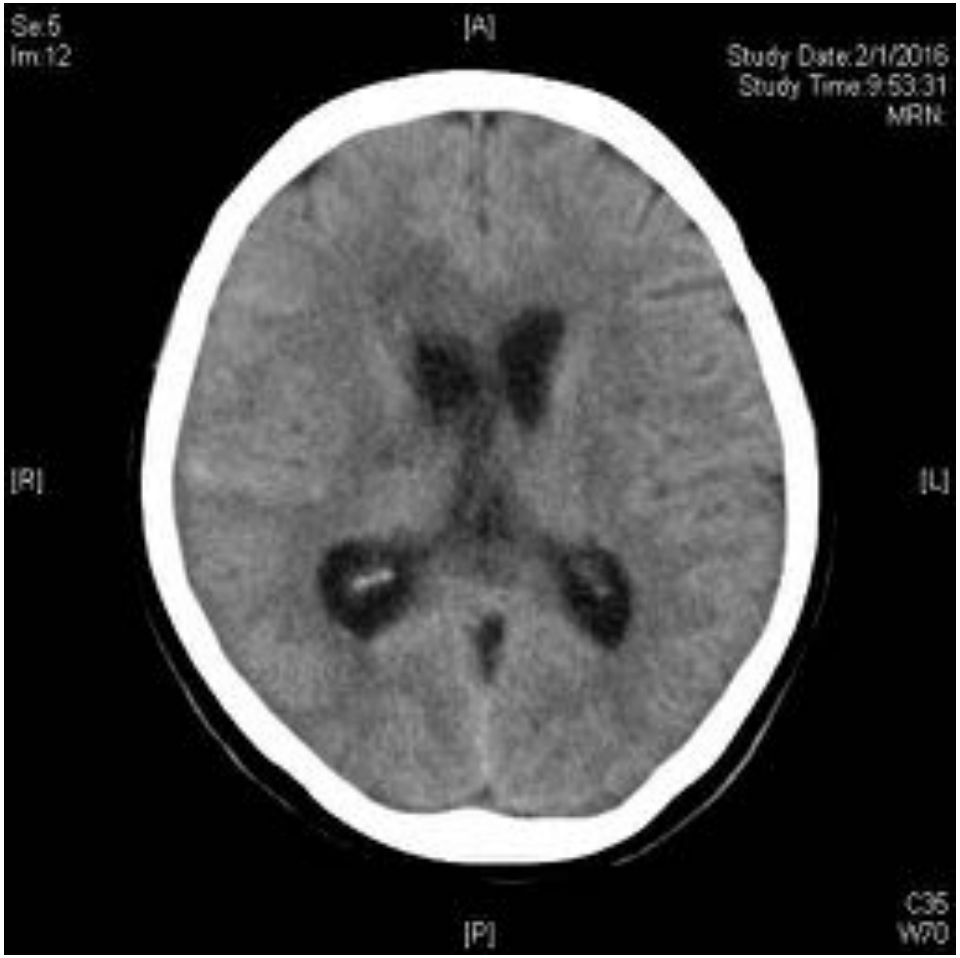
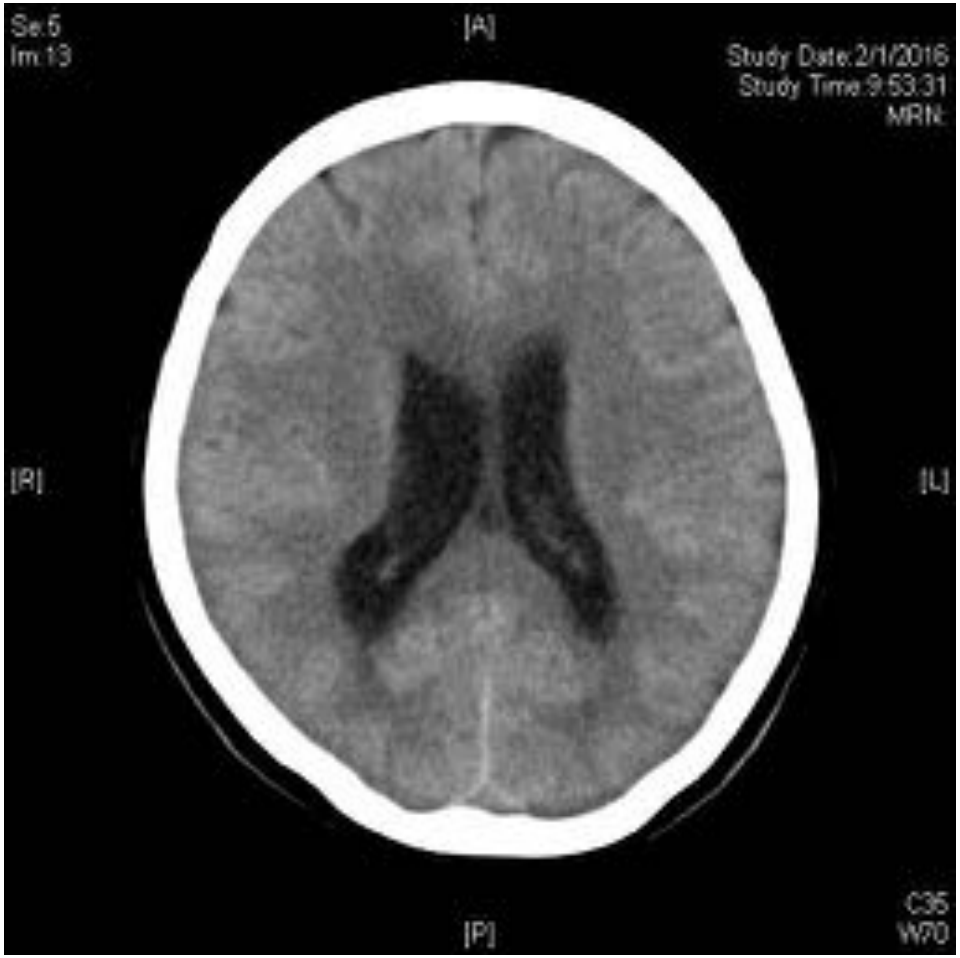


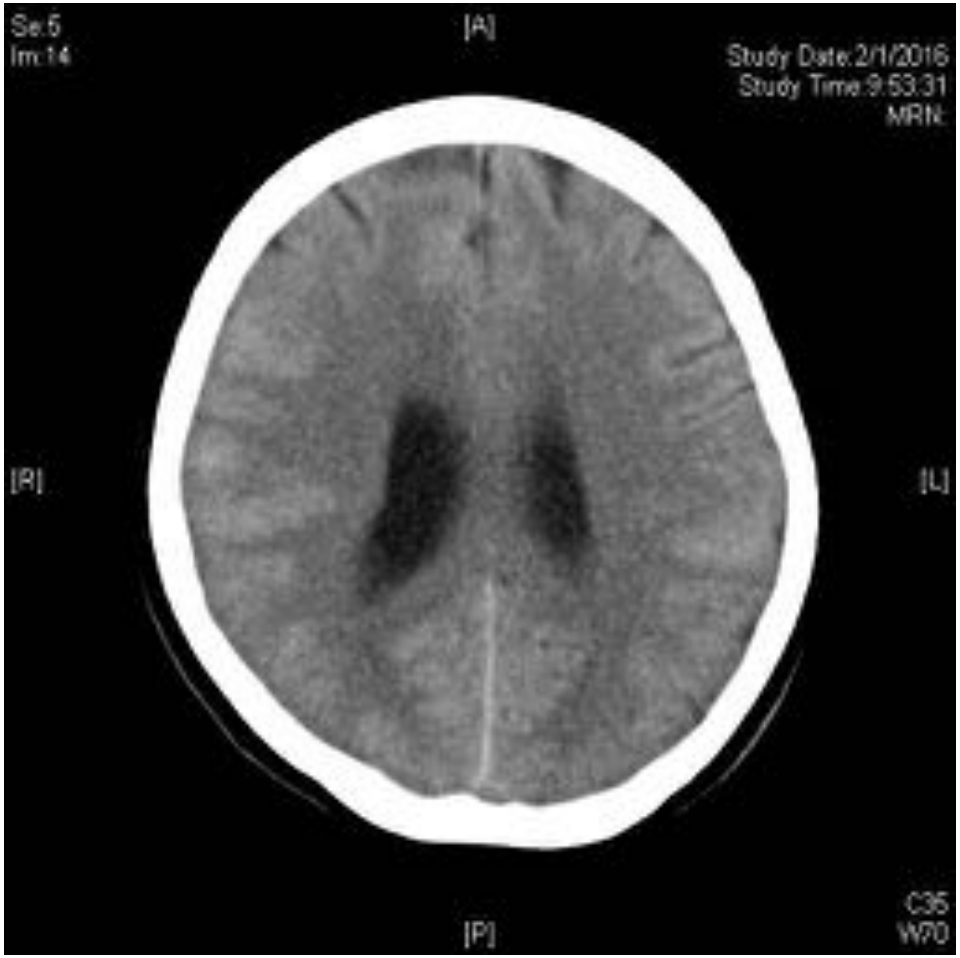
CT brain 02/01/2016



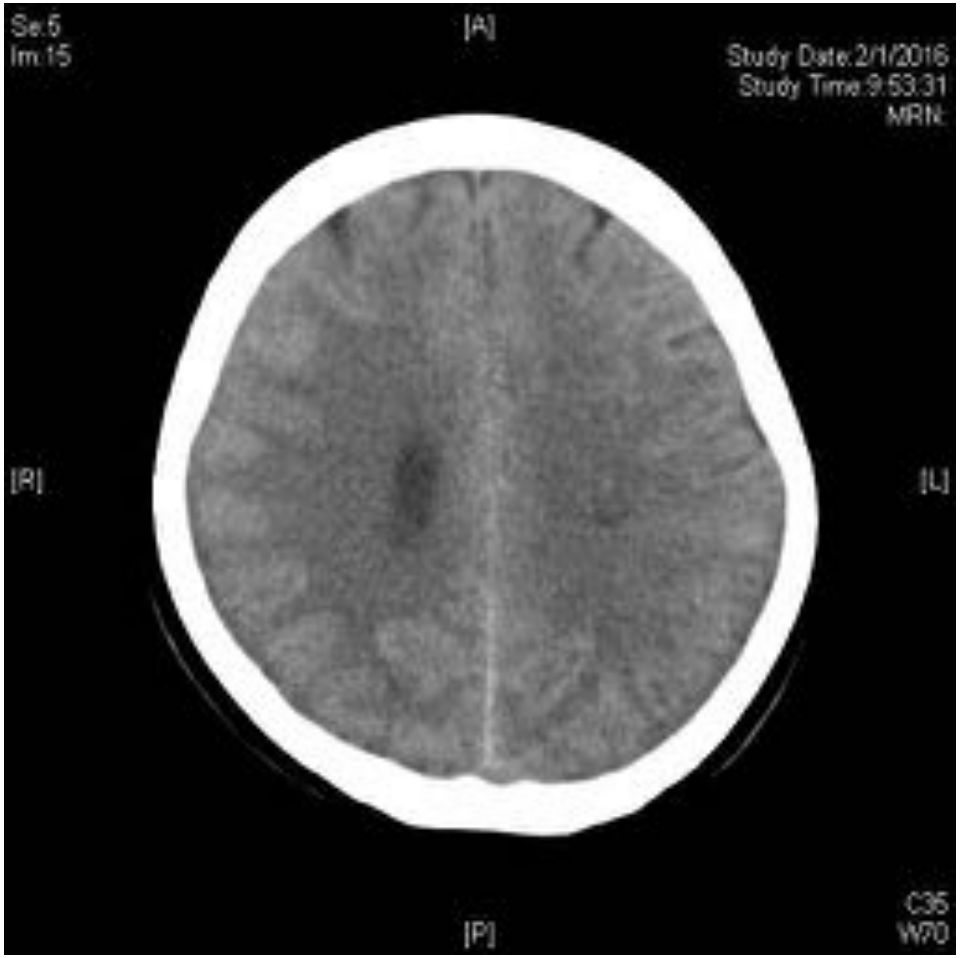
CT brain 02/01/2016



CT brain 02/01/2016



CT brain 02/01/2016



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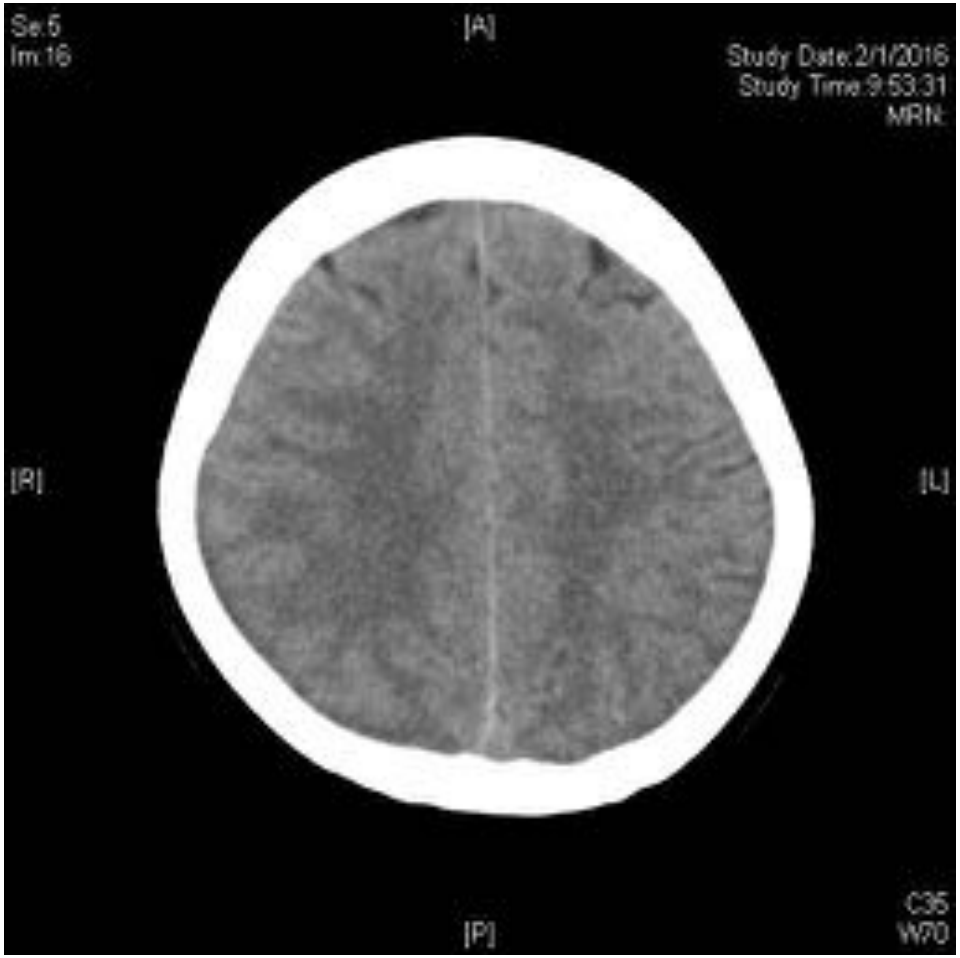
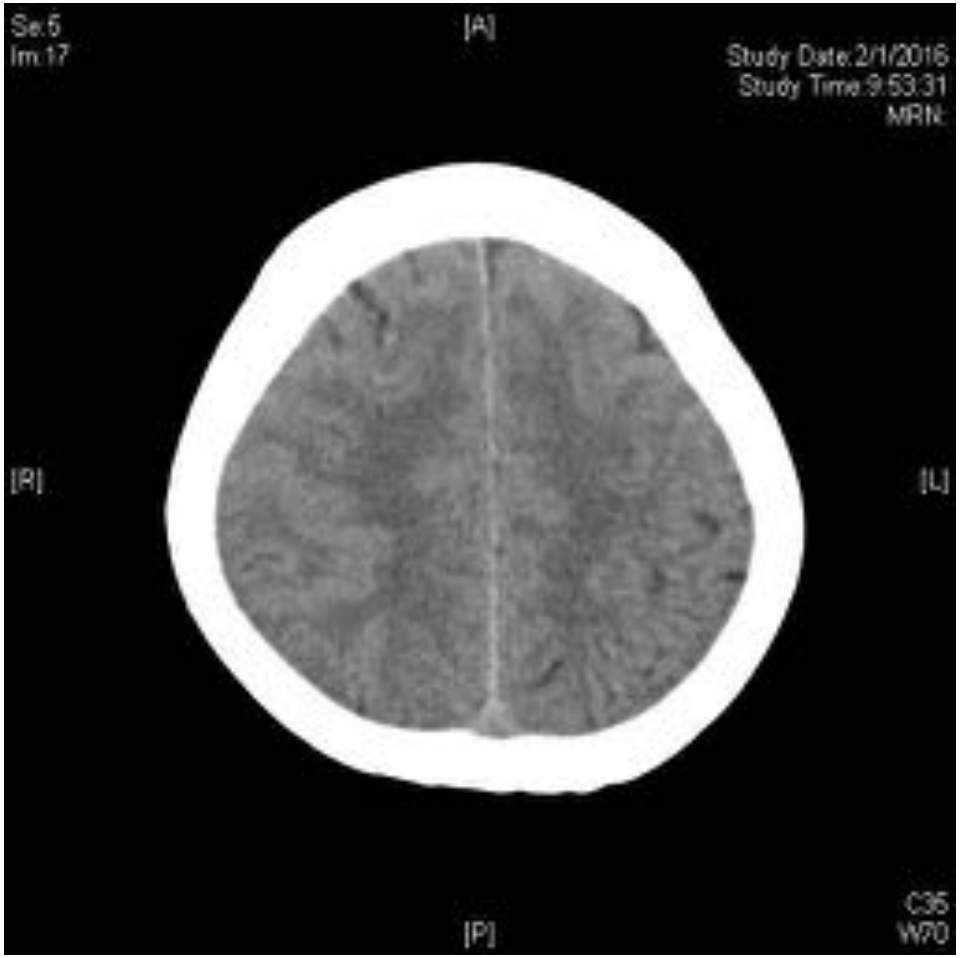


CT brain 02/01/2016



CT brain 02/01/2016

- Definite increase abnormalities in bilateral thalamic regions, right brain stem (and adjacent areas) and corpus callosum etc as reported in MRI on 31/12/2015
- **New hypodense area in LEFT caudate head** which was not seen in MRI on 31/12/2015.
- Ventricles of normal size with no midline shift present.

Taken over by KWH Neurosurgery

Date	

2/1/2016	• Communicating hydrocephalus, suspected TB Meningitis
	• Intra-operative finding:
	  • Slightly turbid CSF drained under high pressure
	  • ICP post drainage of CSF at ear level
	  • Pupils pre- and post-operative right 3mm/ left 2.5mm fixed

3 - 6/1/2016	• Repeated CTs Brain showed progressive infarct in brainstem • Developed diabetes insipidus • Adopted DNACPR and passed away

CSF collected intra-op

Date Collected: 02/01/2016 16:00
Date Arrived: 02/01/2016 16:10
Specimen :- Cerebrospinal fluid (CSF)

Bacterial Antigen :

Streptococcus Group B :	Negative
Haemophilus influenza type B :	Negative
Streptococcus pneumoniae :	Negative
N. meningitidis type B/E.coli K1 :	Negative
N. meningitidis type ACYW135 :	Negative

Microscopy :

Appearance : Clear and colourless

RBC :	203	/cmm
WBC :	221	/cmm
Polymorphs :	81	%
Lymphocytes :	19	%

Gram stain : No organisms seen

Culture :-

No growth obtained

Overview of all Investigations

	29/12	30/12	31/1	1/1	2/1	4/1	5/1	6/1	Reference Range	Units
Urea	4.7	3.8	5.1	6.8	6.1	3.1	3.1	4.5	2.4 – 6.5	mmol/L
Cr	73	77	79	61	50	51	52	96	55 – 103	mmol/L
Na	139	147	159	148	140	139	154	168	136 – 144	mmol/L
K	3.2	3.5	3.9	3.2	3.2	3.9	3.2	5.6	3.3 – 4.6	mmol/L
Calcium	2.10		2.12	1.91	1.93				2.07 – 2.37	mmol/L
PO4	1.10		0.65	0.73	0.65				0.83 – 1.43	mmol/L
Bilirubin	17	20	23	12	12				1.7 – 5.8	umol/L
ALP	58	78	80	61	59				1.0 – 3.1	U/L
ALT	583	400	315	196	148				< 46	U/L
Albumin	32	32	27	22	21				37 – 47	U/L
Globulin	34	41	39	34	36				25 - 39	U/L

Overview of all Investigations

	29/12	30/12	31/12	1/1	2/1	3/1	4/1	5/1	Reference Range	Units
WBC	17.0	15.1	18.0	17.7	20.9	20.1	18.2	17.3	3.70 – 9.20	X 10^9/L
RBC	4.64	5.24	4.8	3.7	3.42	3.24	3.42	3.50	4.30 – 5.90	X 10^{12}/L
HGB	13.8	15.7	14.4	11.2	10.7	10.0	10.7	10.6	13.40 – 17.10	g/dL
PLT	209	223	214	182	177	180	216	226	145 – 370	X 10^9/L
Neu	14.2	12.7	15.0	15.2		17.1	17.3	15.7	1.7 – 5.8	X 10^9/L
Lym	1.0	0.9	1.3	1.1		1.4	0.4	0.5	1.0 – 3.1	X 10^9/L
Mon	1.8	1.4	1.7	1.3		1.6	0.4	0.9	0.0 – 0.5	X 10^9/L

Other workup

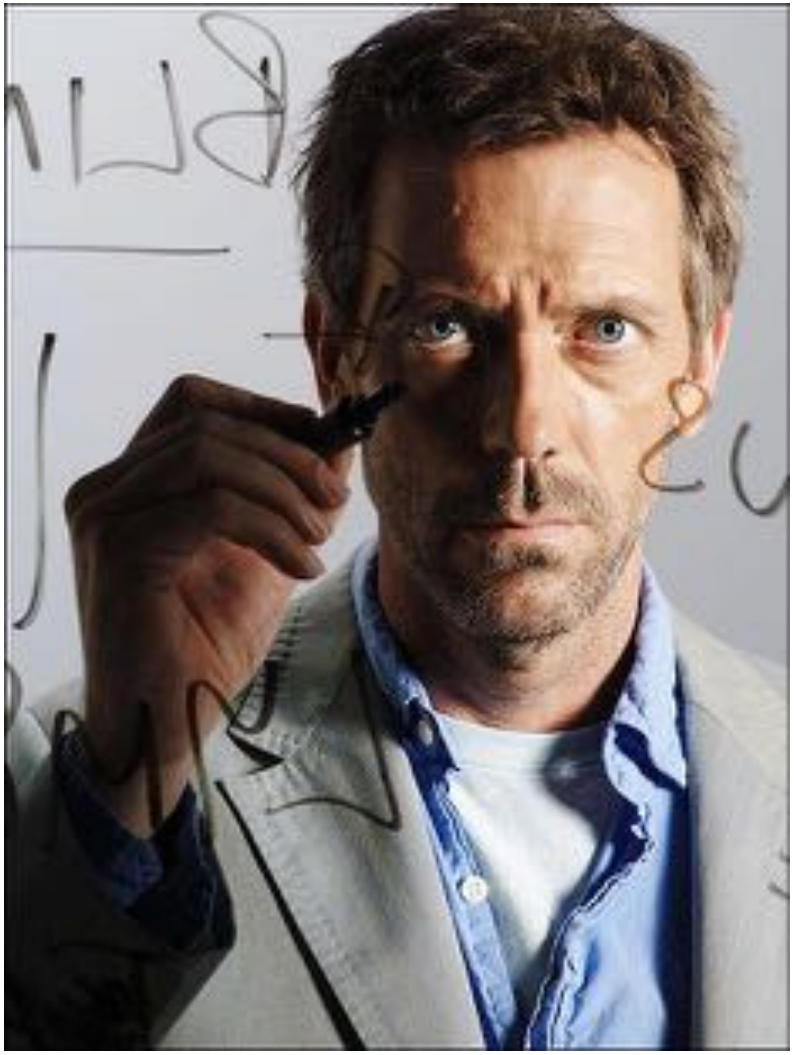
- CSF, Tracheal aspirate, Early morning – TB culture negative
- CSF Fungal culture, bacterial culture, Syphilis, cytology NEGATIVE (inflammation, no malignant cell)
- Anti-HAV, HbsAg, Anti-HCV, Anti-HIV negative
- Blood culture negative x3
- Anti-aquaporin-4 and ANCA negative
- Echocardiogram negative for vegetation

Outcome

- Referred to coroner with whole body autopsy done

Clues so far

- Optic neuritis
- CSF suggestive of CNS infection/inflammation
- Progressive stroke in brainstem and thalamus
- Erythema nodosum



Infective causes of stroke

Organism	Infection	Mechanism
Bacterial infection		
Treponema pallidum	Neurosyphilis	Vasculitis
Mycobacterial tuberculosis	Tuberculous meningitis	Arteritis; Meningitis; Arachnoiditis
Chlamydia pneumoniae	Acute or chronic respiratory infections	Accelerated atherogenesis, enhanced platelet aggregation
Helicobacter pylori	Gastritis, peptic ulcer disease	Enchanced platelet aggregation, prothrombotic state
Parphyromons gingivalis (and other periodontal pathogens)	Periodontal disease	Chronic inflammation due to infectious burden; prothrombotic state
Parasitic infection		
Trypanosoma cruzi	Chagas disease, Heart failure	Cardioembolism
Taenia solium	Neurocysticercosis	Arachnoiditis/small artery vasculitis; direct compression of large arteries by cysts
Plasmodium falciparum	Cerebral malaria	Occlusion of cerebral arteries by infected erythrocytes
Echinococcus granulosis	Cardiac hydatidosis	cerebral cystic echinococcosis
Schistosoma mansoni	Schistosomiasis	Microembolic borderzone infarction
Toxocara canis	Toxocariasis	Arachnoiditis; vasculitis
Spirometra species (tapeworm)	Neurotrichinelliasis	Microinfarction due to direct obstruction of small vessels with larvae; vasculitis

Miller EC, Elkind MS. Infection and Stroke: an Update on Recent Progress. Current neurology and neuroscience reports. 2016;16(1):2.

Infective causes of stroke

Organism	Infection	Mechanism
Fungal infection		
Cryptococcus	Systemic and CNS infections (Usually immunocompromised)	Meningitis; vasculitis
Aspergillus	Systemic and CNS infections	Arteritis, vasculopathy
Mucorales (including Rhizopus, Mucor, etc.)	Mucormycosis	Vascular invasion of fungus, aneurysmal dilatation, vascular necrosis
Viral infection		
Human immunodeficiency virus (HIV)	HIV disease/AIDS	Vasculopathy; susceptibility to opportunistic CNS infections
Cytomegalovirus	Often asymptomatic, latent; occasional mononucleosis-like syndrome	Inflammatory response with accelerated atherogenesis
Varicella zoster virus	Chickenpox, shingles	Vasculitis/vasculopathy
Herpes simplex virus (types 1 and 2)	Oral and genital infections	Vasculopathy; possible stroke trigger in young people
Parvovirus B19	Fifth disease	Possible arteriopathy

Miller EC, Elkind MS. Infection and Stroke: an Update on Recent Progress. Current neurology and neuroscience reports. 2016;16(1):2.

Differential diagnosis of Optic neuritis

- *Unilateral ON*
  - Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)
  - Infectious/ inflammatory
    - Neuroretinitis
    - Viral
    - Post- viral
    - Fungal
    - Syphilis
    - Toxoplasmosis
    - Lyme
    - Herpes zoster
    - Sarcoidosis
    - T.B.
    - Collagen vascular disease
    - Autoimmune ON
  - Leber's hereditary ON
  - Compressive
    - Meningioma
    - Glioma
    - Metastasis
    - PNS mass
  - Infiltrative
    - Multiple myeloma
    - Leukemia
  - Retinopathies
    - Paraneoplastic ON
    - Cone dystrophy

Erythema nodosum

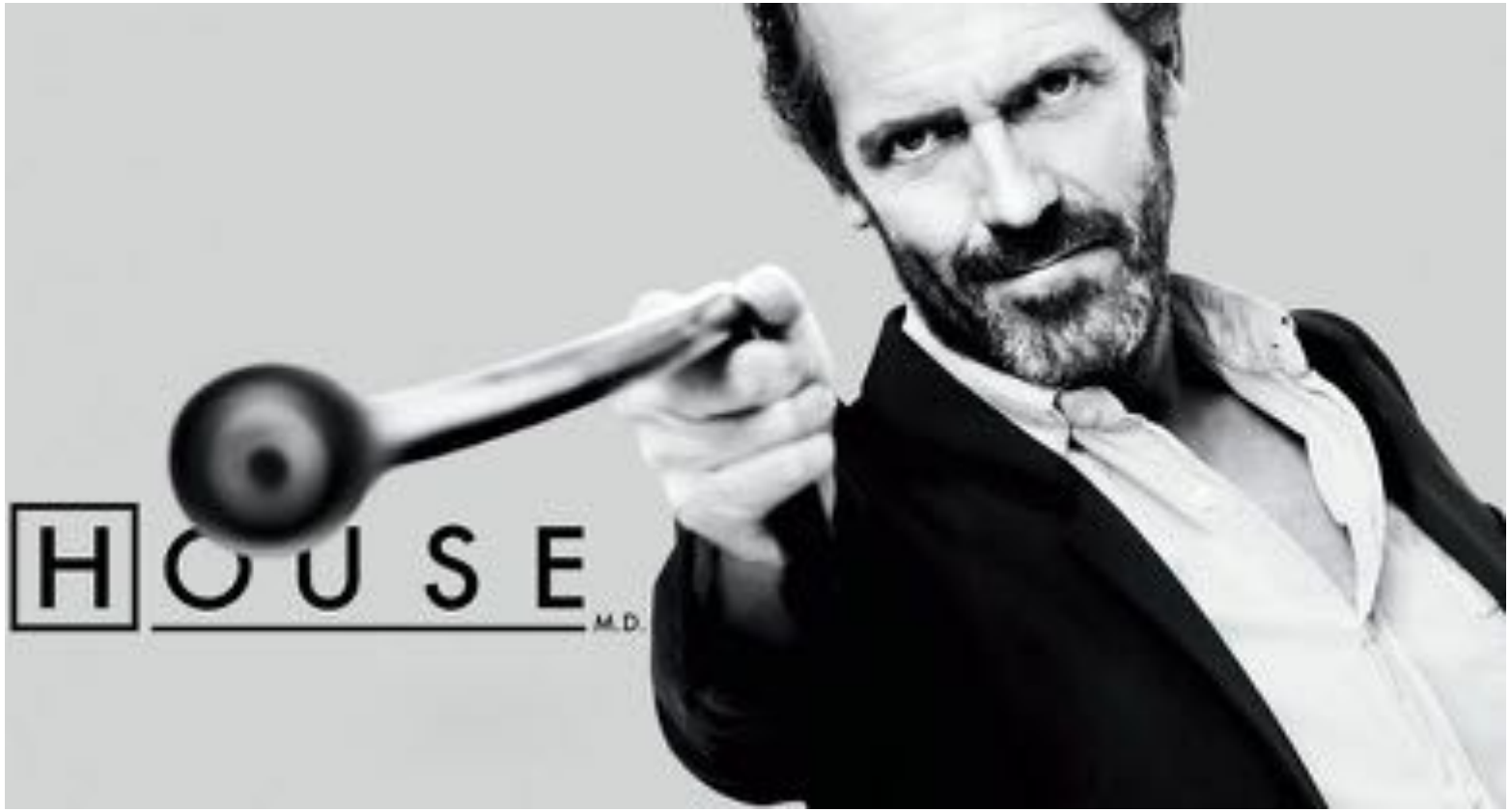
- **NO** cause is found in 60% of cases
- **D**rug (iodides, bromides, sulfonamides, NSAID)
- **O**estrogen (Oral contraceptives, pregnancy)
- **S**arcoidosis
- **U**lcerative colitis, Crohn's disease, Behçet's
- **M**icrobiology: any chronic infection (bacterial, viral, yersinia, tuberculosis, leprosy, deep fungal)

Typical and atypical presentations of inflammatory optic neuritis

Typical signs and symptoms of optic neuritis0	Red flags: atypical signs and symptoms of optic neuritis
Young adult patient <50 years old	Age >50 or <12 years
Acute or subacute visual loss	Sudden visual loss
Progressive over a few days up to 2 weeks	Progressive visual loss for >2 weeks
Unilateral visual loss with reduced colour and contrast vision, any type of visual field defect	Severe visual loss to no perceptions of light
	Bilateral visual loss
Periocular pain and painful eye movement	No pain
	Severe or persistent pain >2 weeks
Previous history of ON or MS	Previous history of neoplasia
Neurological signs and symptoms suggestive of MS	Clinical symptoms suggestive of other diseases than MS (NMO, connective tissue disorders, sarcoidosis, vasculitis)
Normal or swollen optic disc	Severe optic disc oedema
Normal macula and peripheral retina	Optic disc haemorrhage
Uveitis or retinal periphlebitis possible	Marked uveitis or retinal periphlebitis
Spontaneous improvement after 2 - 3 weeks	Absence of recovery >3 weeks after onset
	Optic atrophy without history of ON or MS
No deterioration after withdrawal of steroids	Deterioration after withdrawal of steroids

Voss E, Raab P, Trebst C, Stangel M. Clinical approach to optic neuritis: pitfalls, red flags and differential diagnosis. Therapeutic advances in neurological disorders. 2011;4(2):123-34.

What is the diagnosis?



Pathology Report

CNS :

- Blurred hole was done,
- Vertebral/ carotid arteries : NAD
- Subdural clot : 1cm over cerebellum & pons
- Multiple whitish-yellow sub-centimeter nodules in ventral surface of mid-brain and pons.
- Haemorrhagic area in R pons & R thalamic region extending to corpus callosum.
- SAH in R frontal-temporal region, L temporal, L pontine region
- No brain tumor

Abdomen :

- No ascites, adhesion in omentum, no peritonitis,
- Stomach/intestine/esophagus : NAD
- No liver cirrhosis, portal vein : no thrombus
- Gallbladder/pancreas : NAD
- Kidneys : cortical cyst in right kidney, ureter/bladder : NAD

Gross exam :

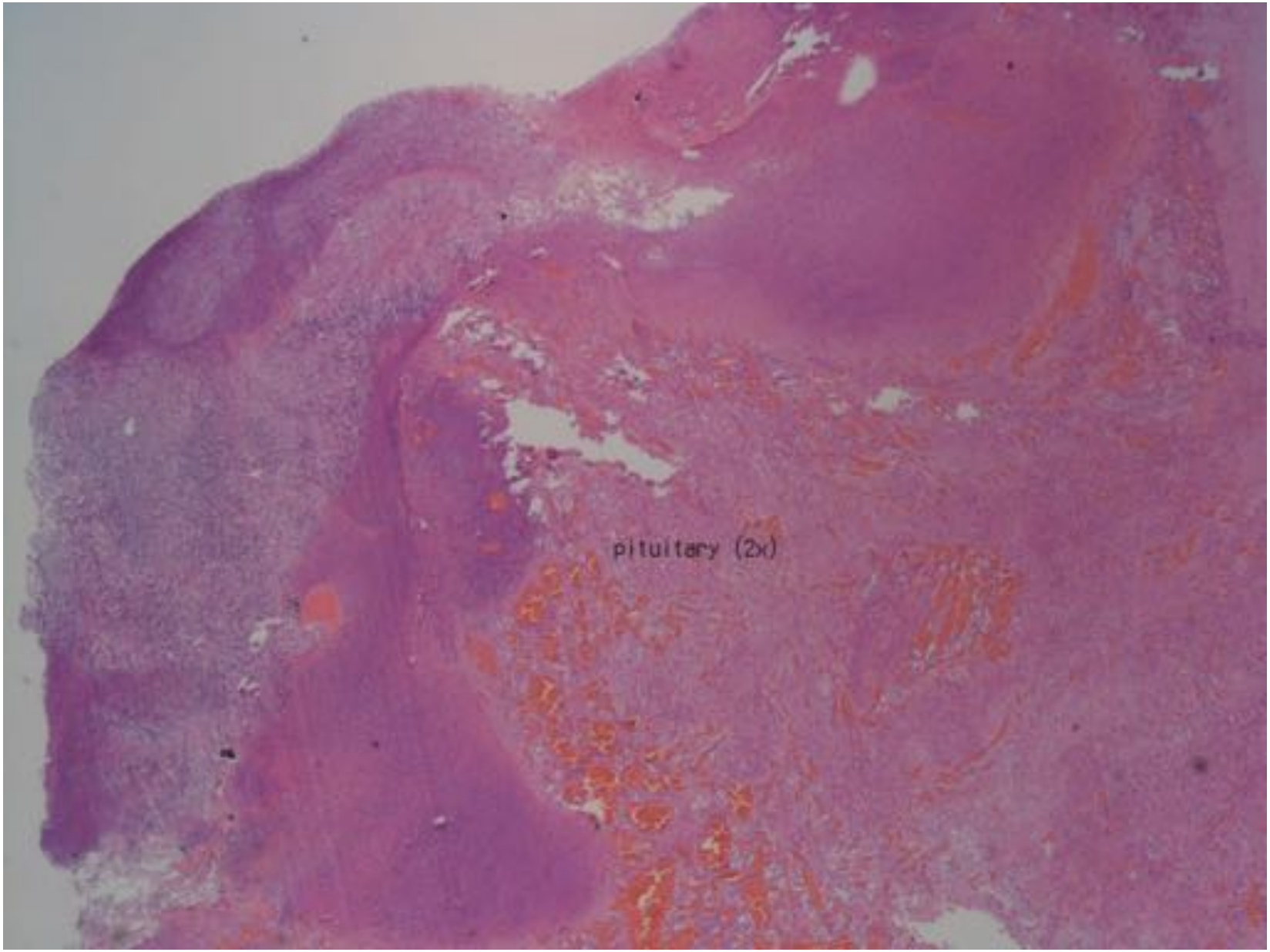
- CVS : no pericardial effusion, smooth pericardium,normal size heart, chamber not dilated, myocardium : homogenous, stain : no infarct, patent coronary arteries, aorta : mild atherosclerosis

Resp. :

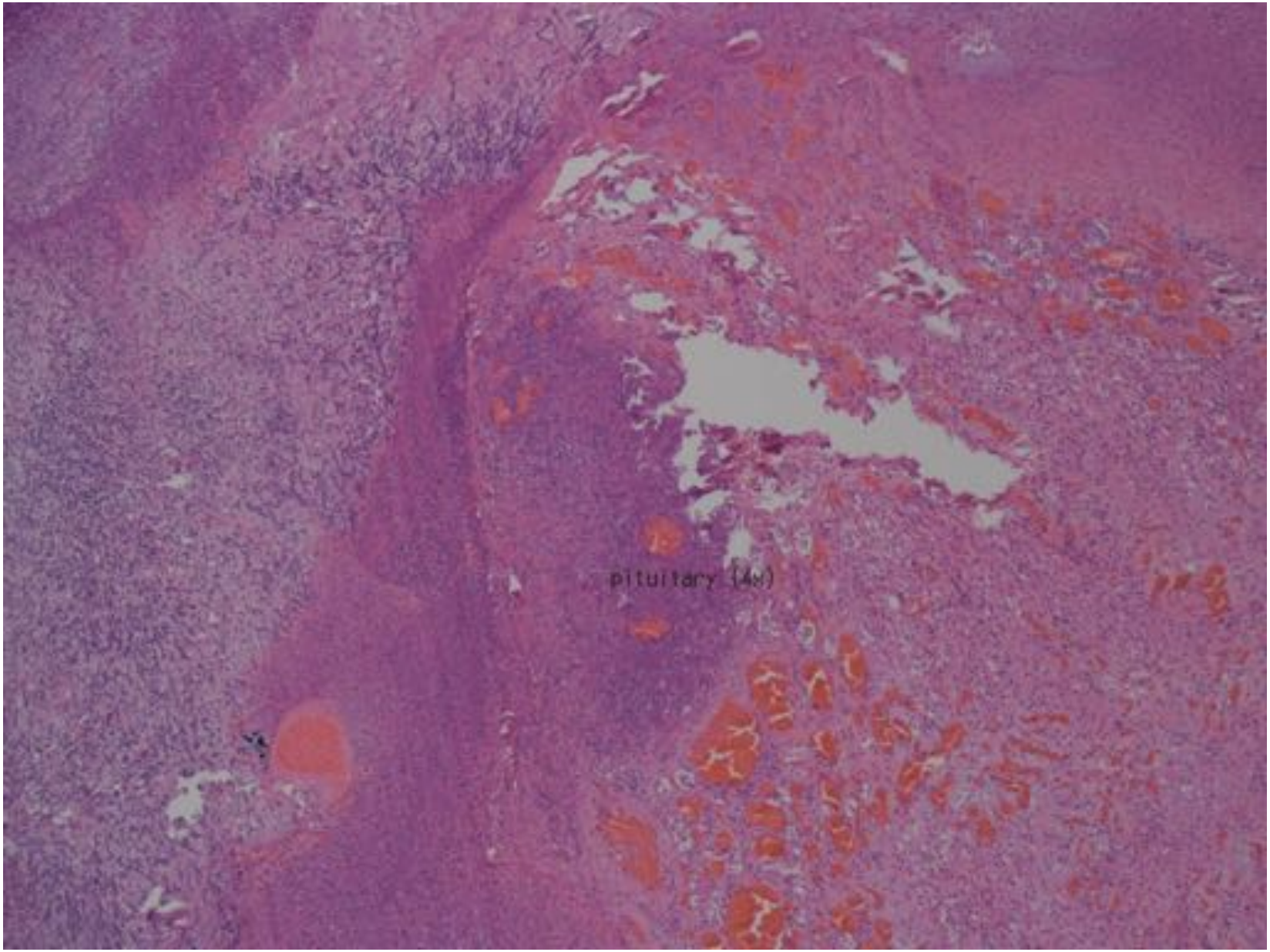
- No pleural effusion, no tumour/infarct/consolidation
- Vasculature : no pulmonary embolism
- Lungs : 300-400gm (normal)

Endocrine :

- Thyroid : light yellow nodules
- Pituitary / adrenal glands : NAD



Courtesy of Dr. SY CHU, Pathology, Kwong Wah Hospital



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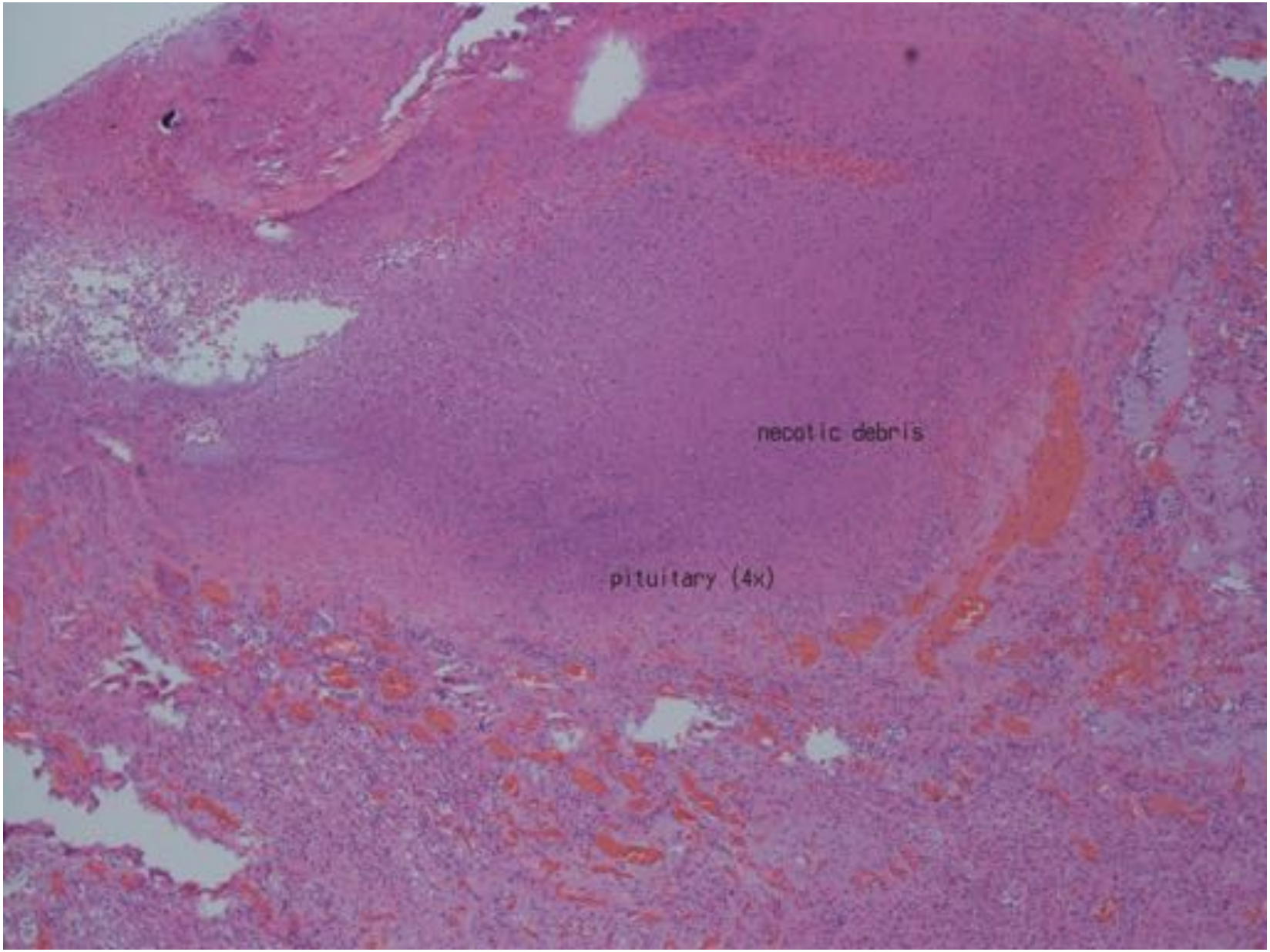

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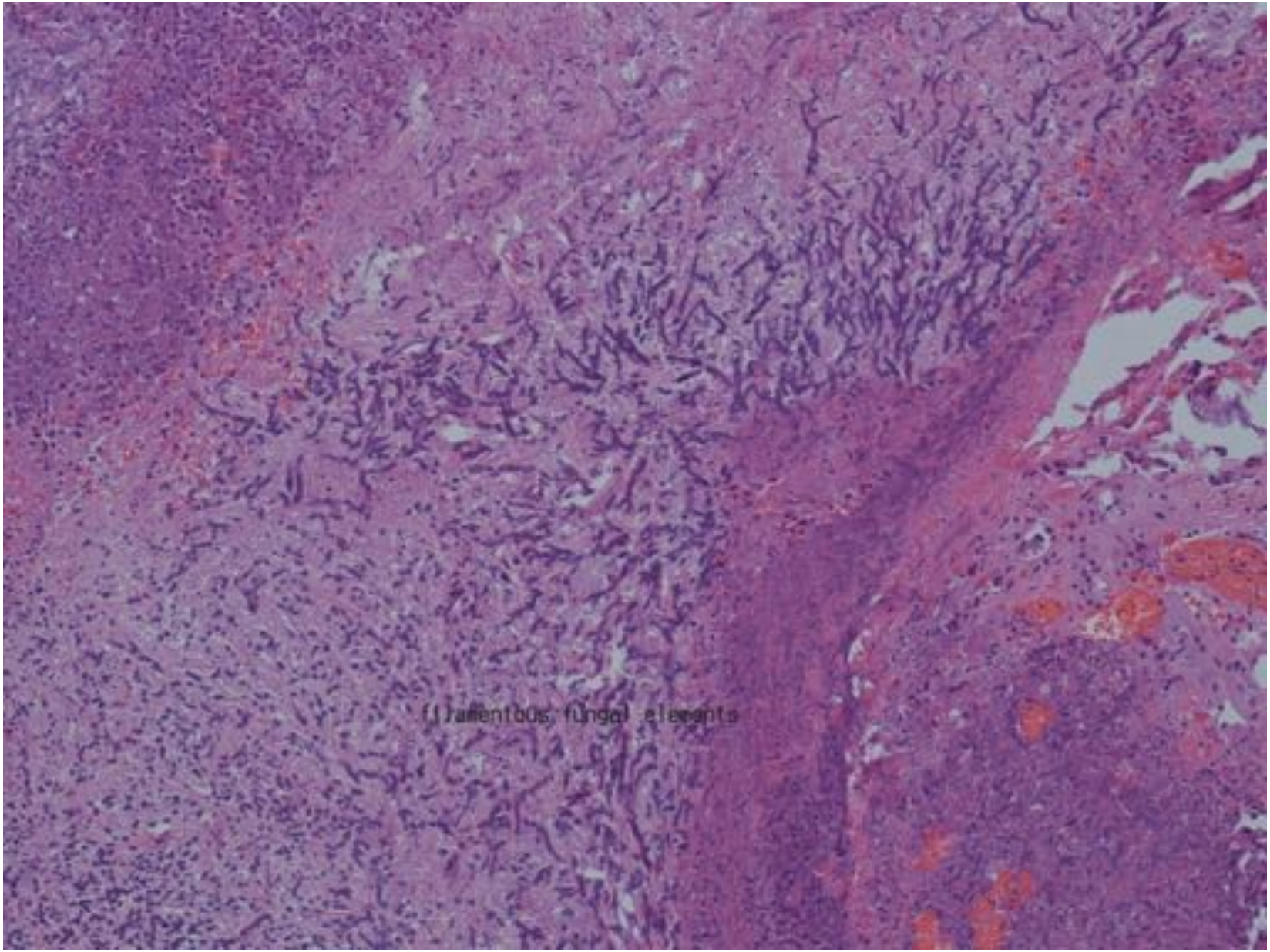

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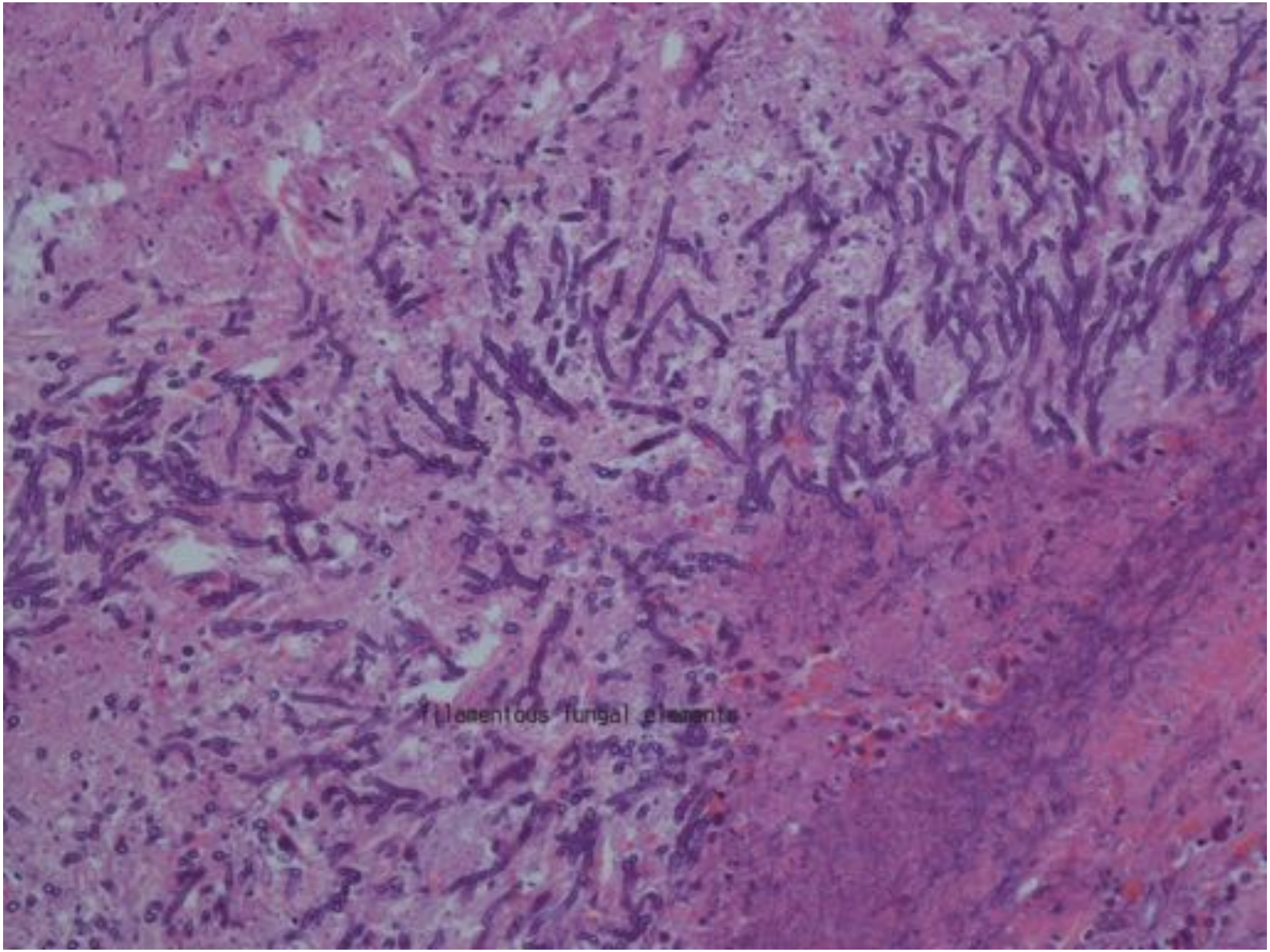

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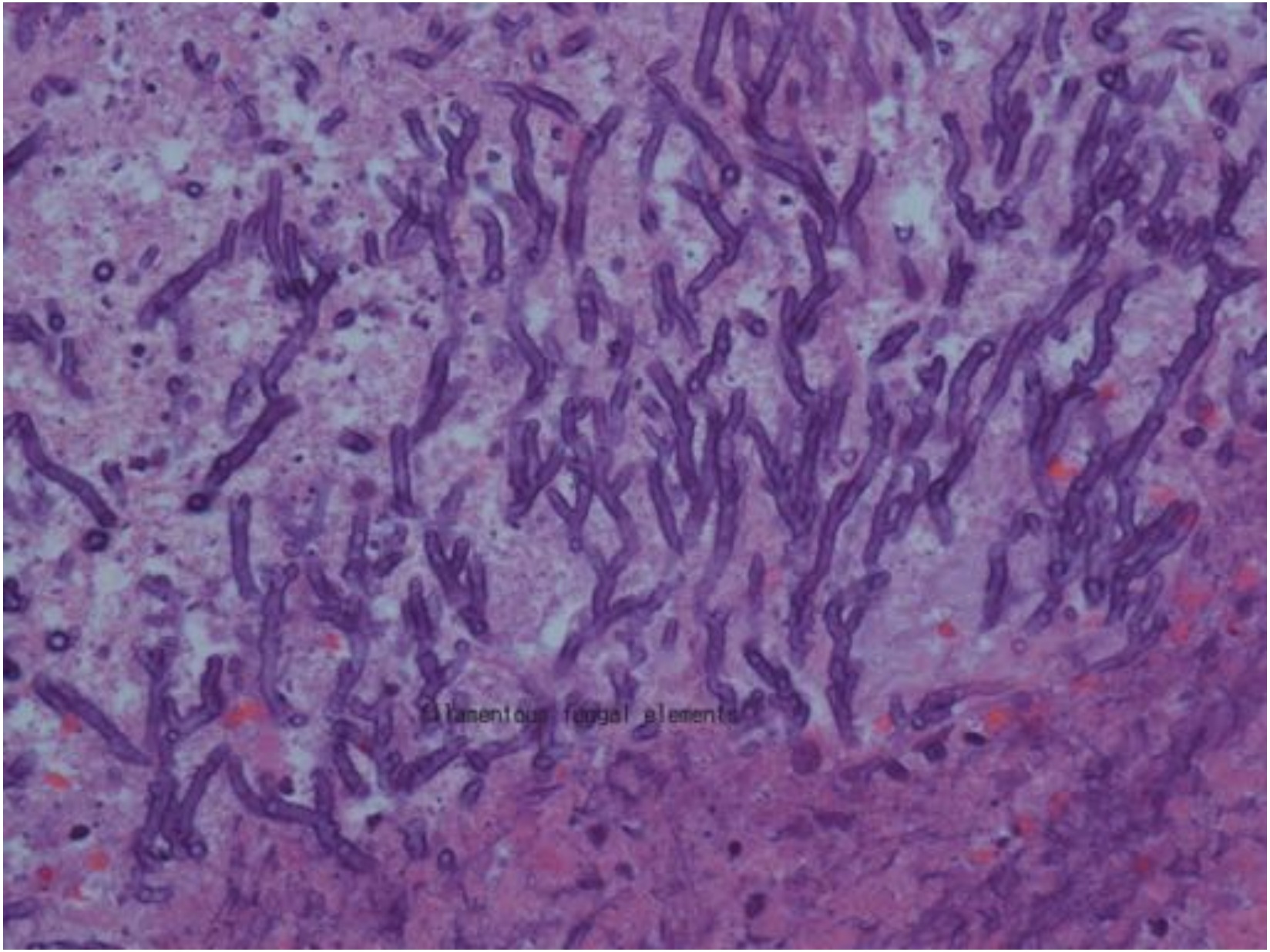

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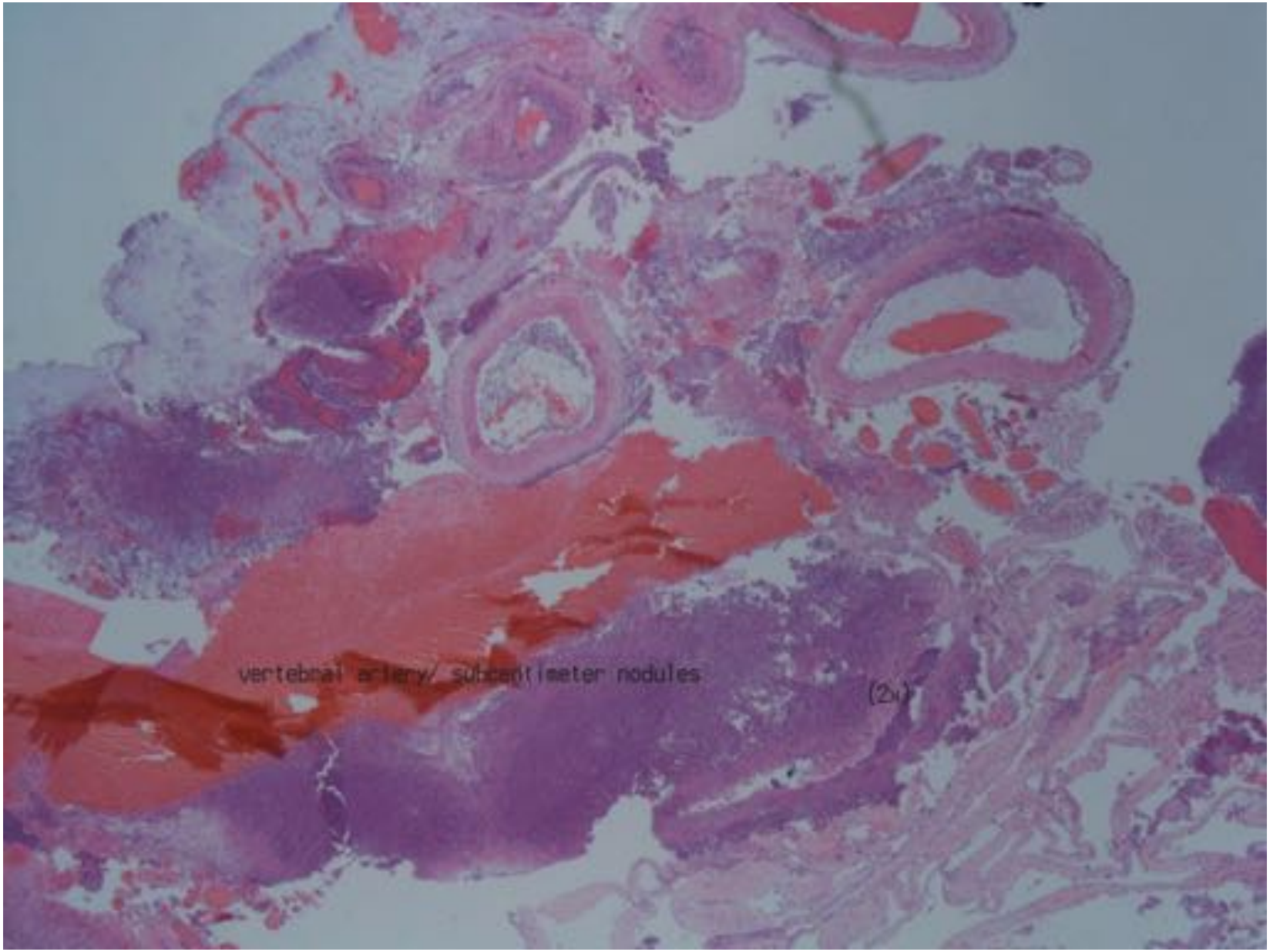

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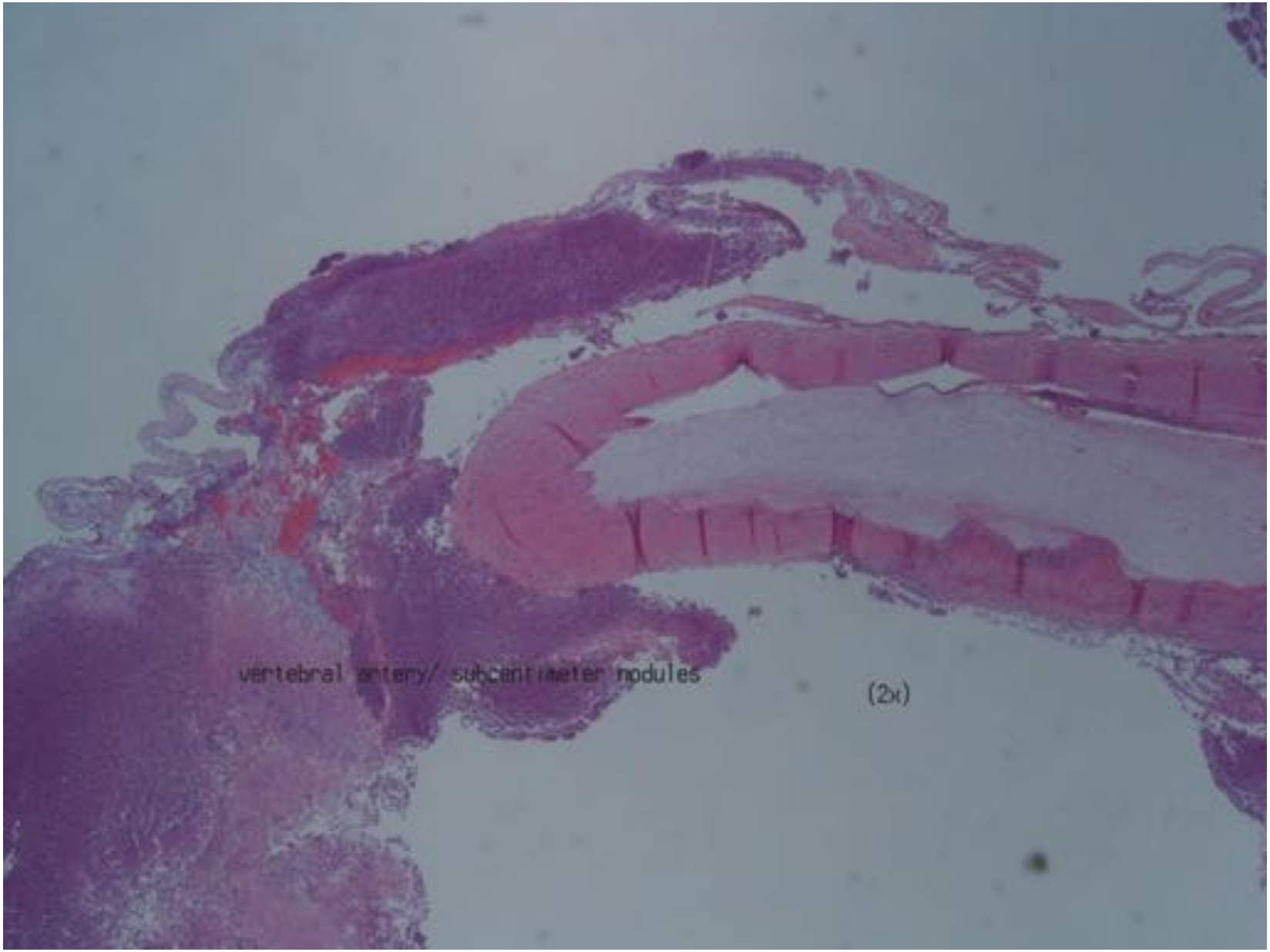

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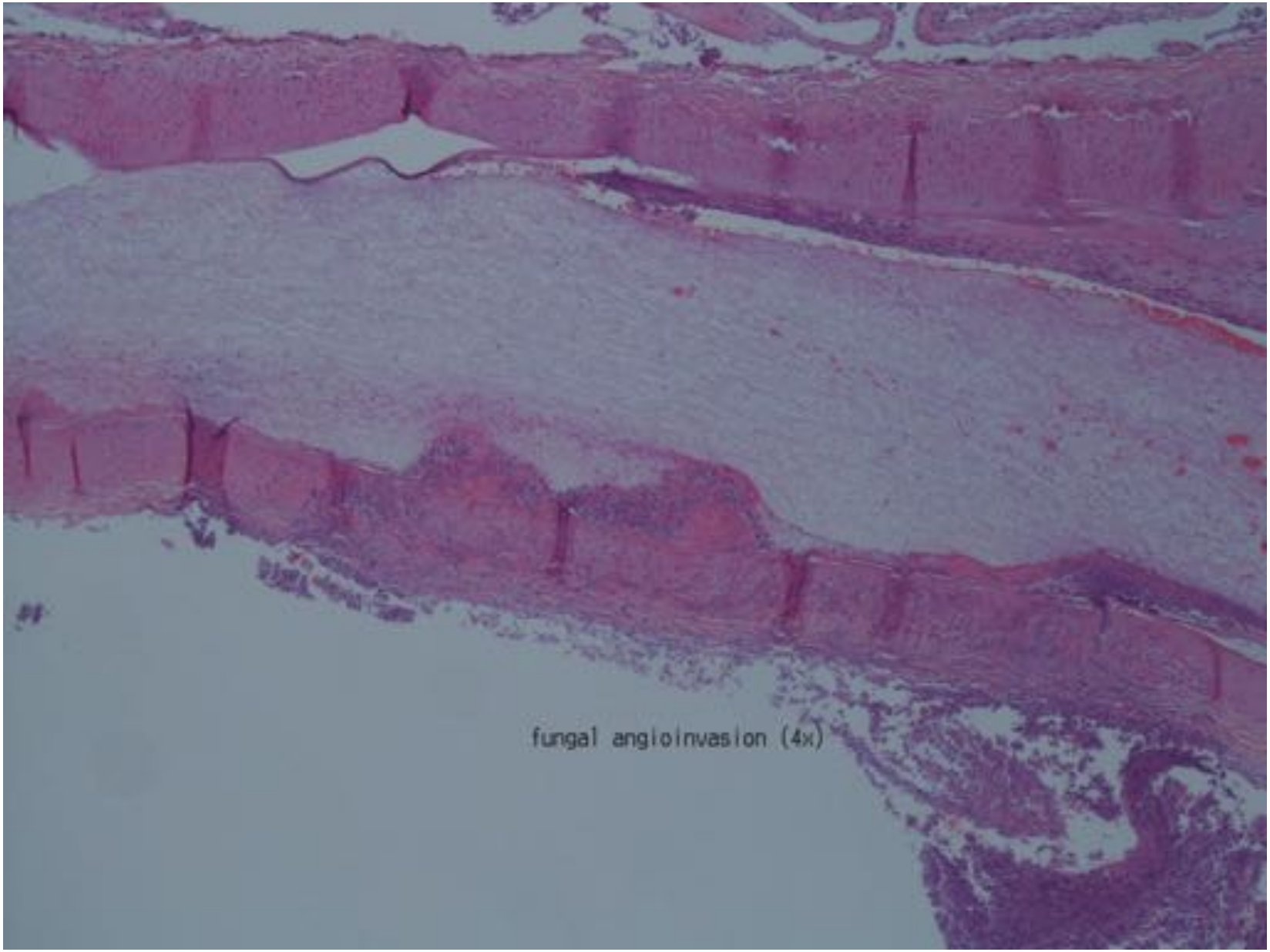

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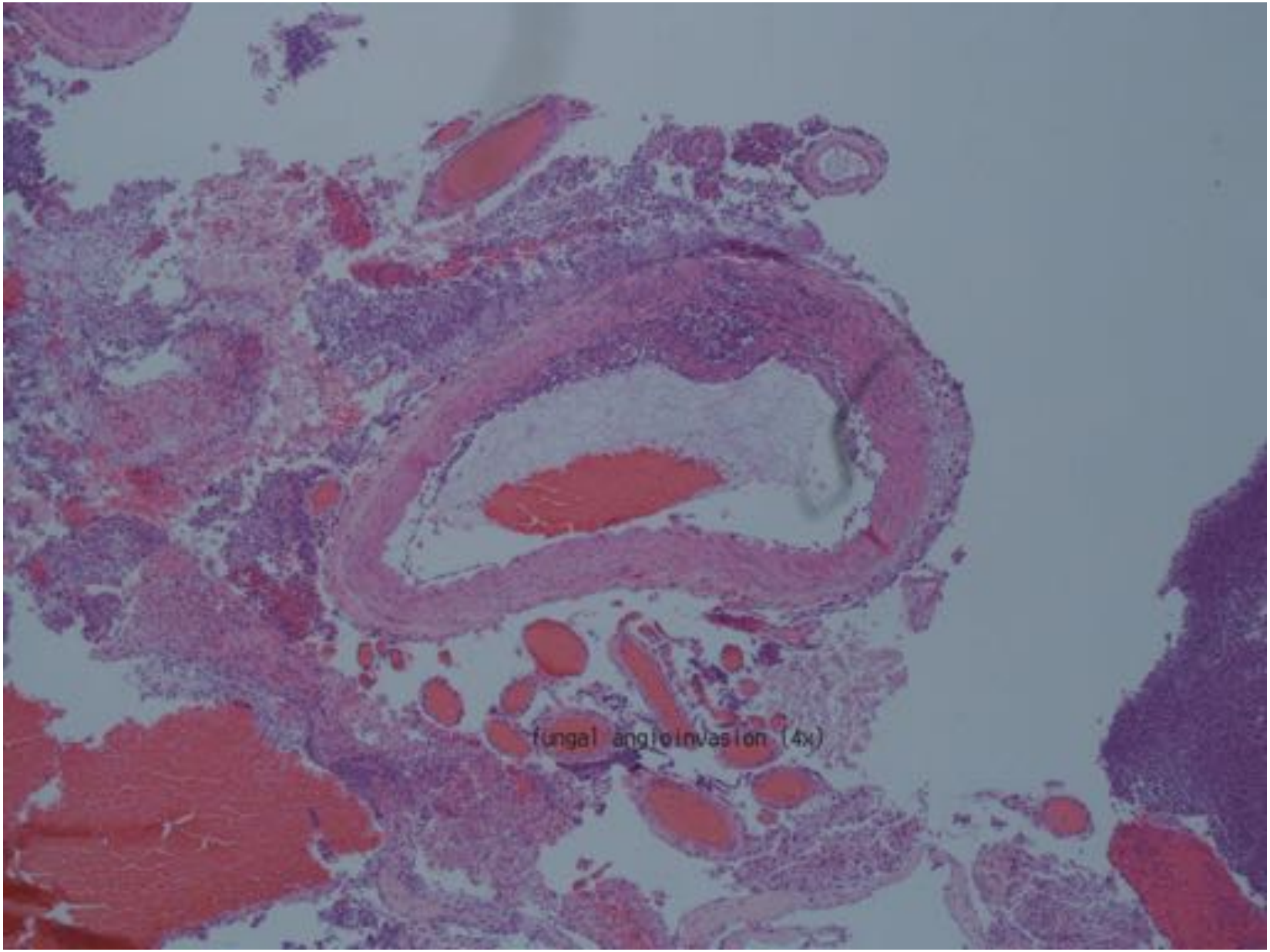

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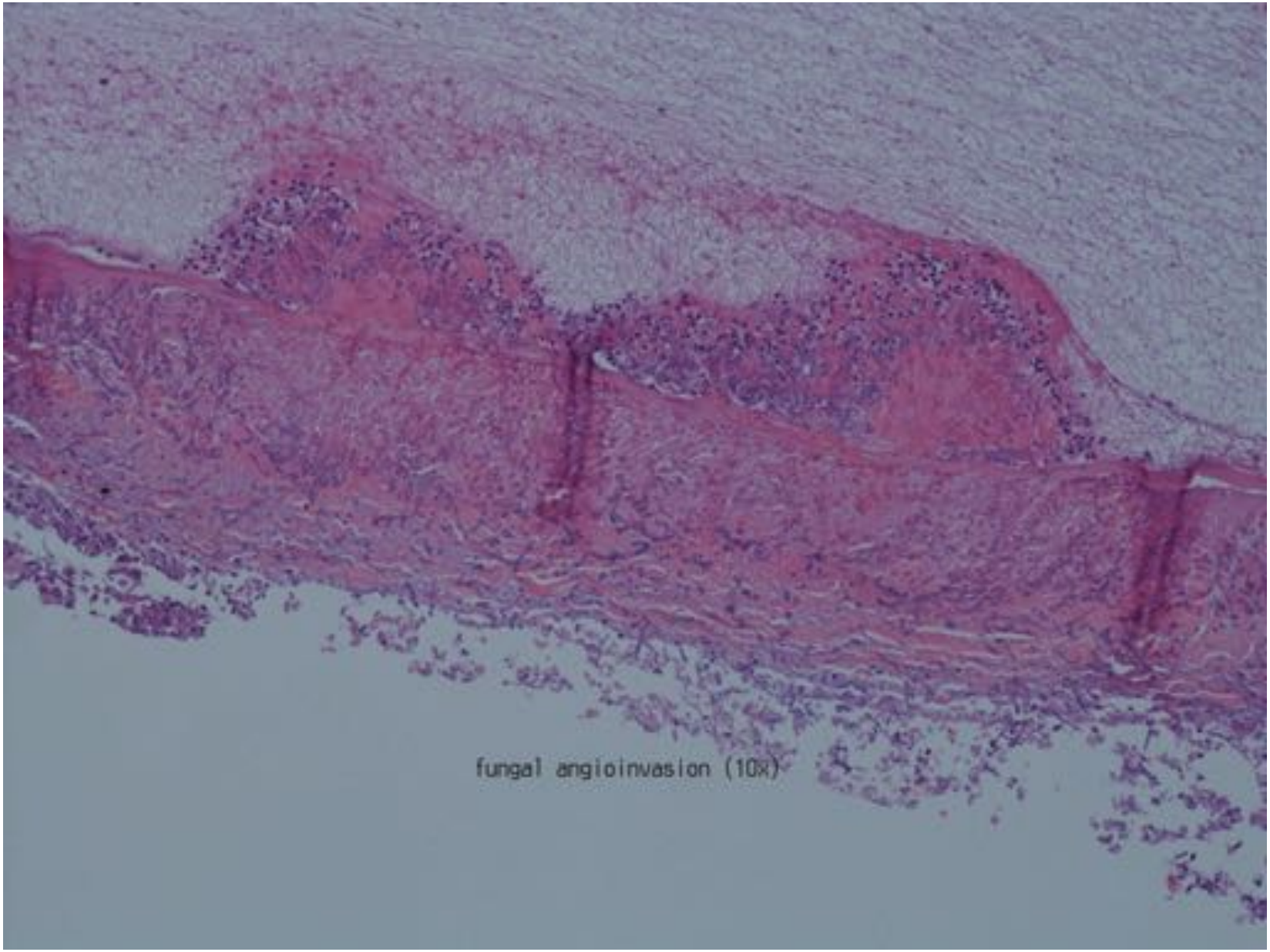

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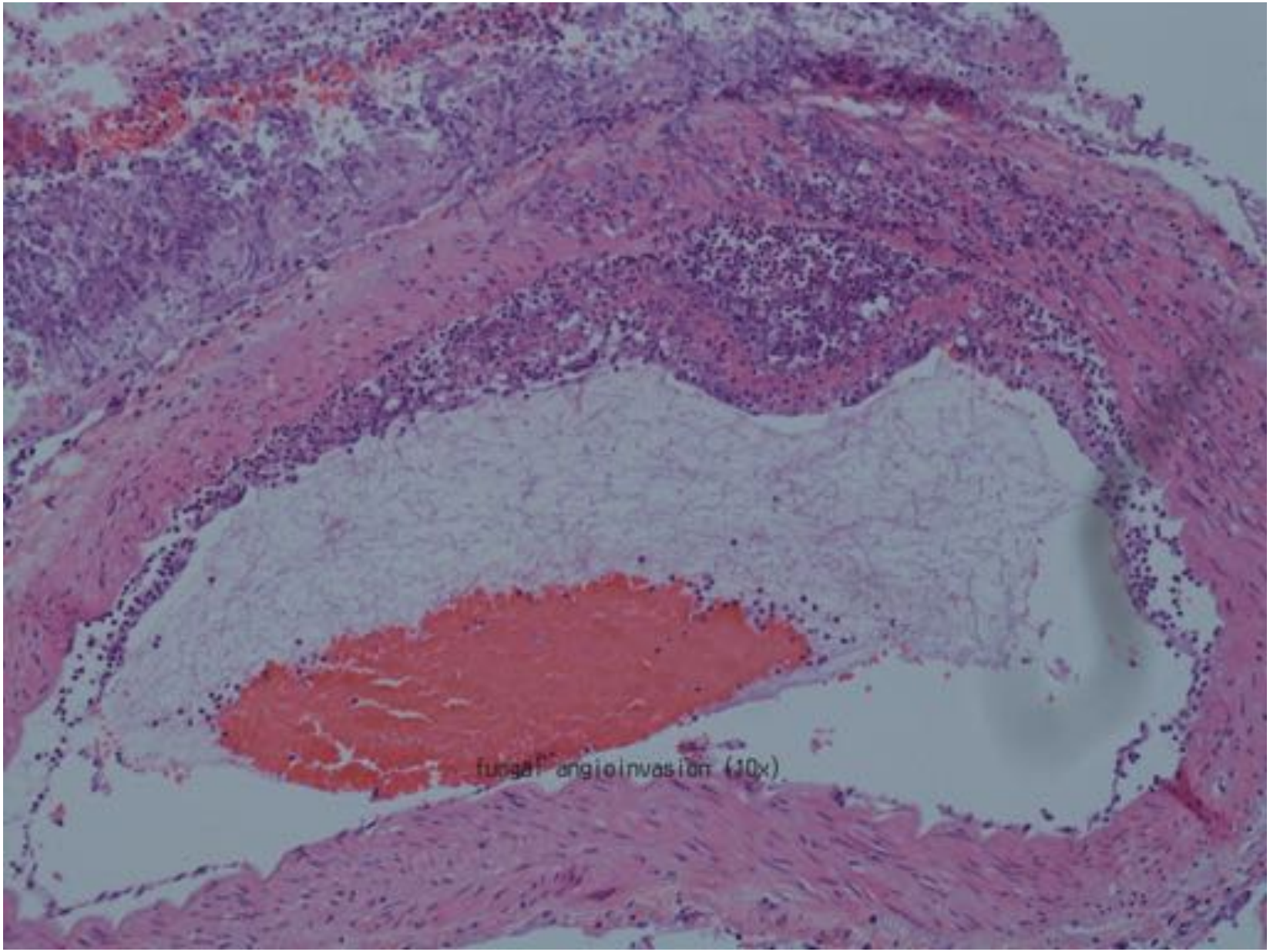

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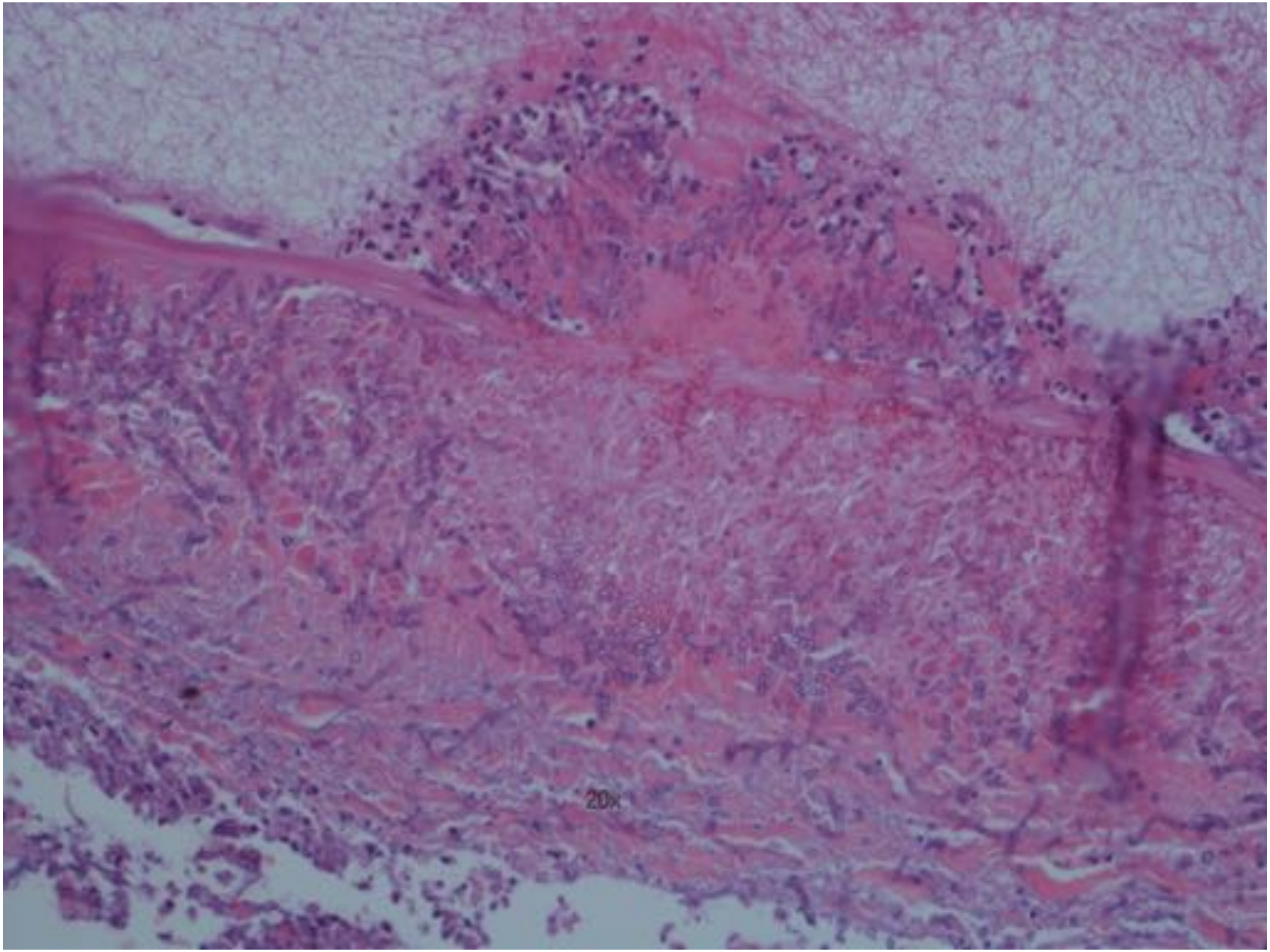

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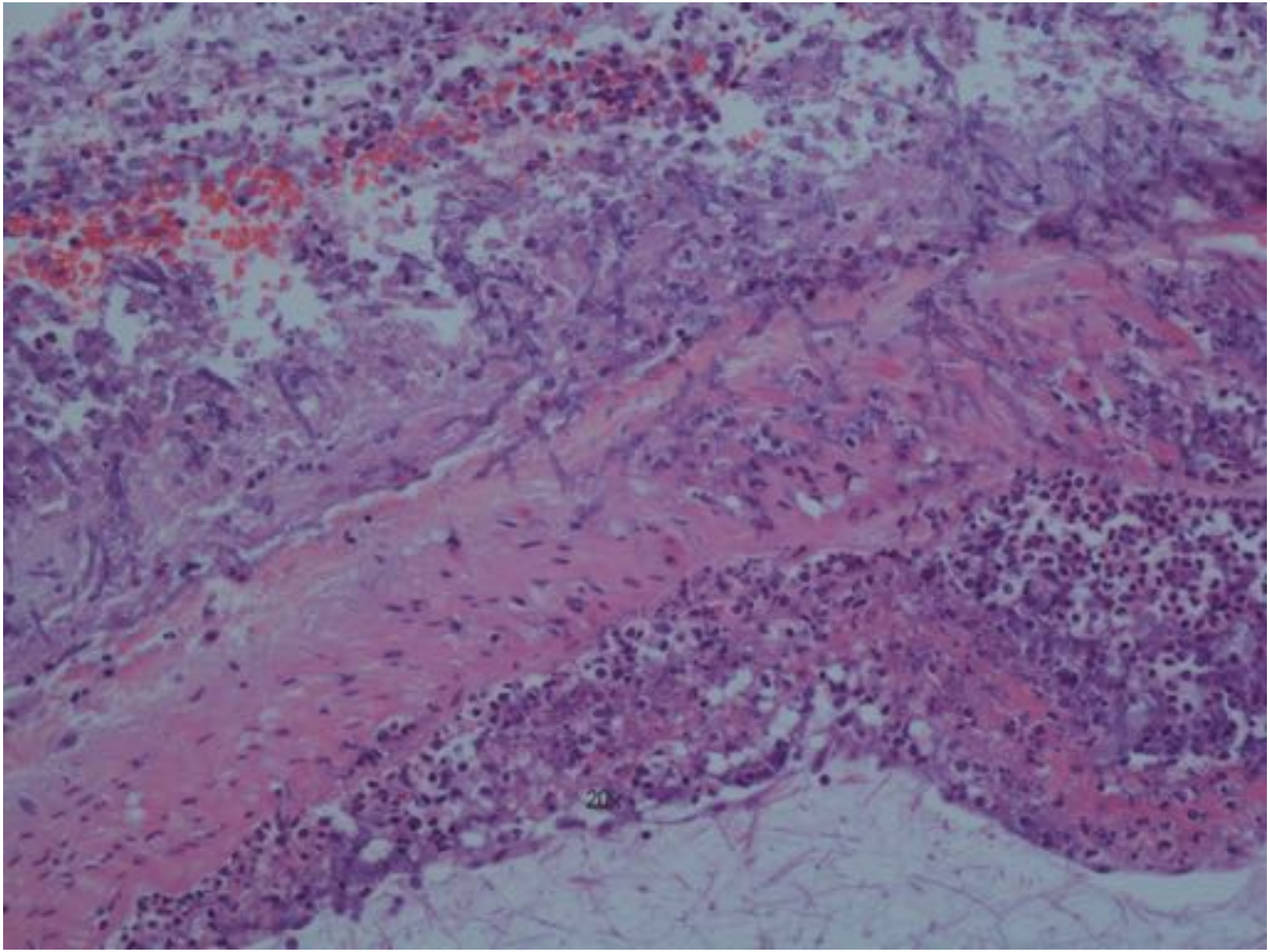

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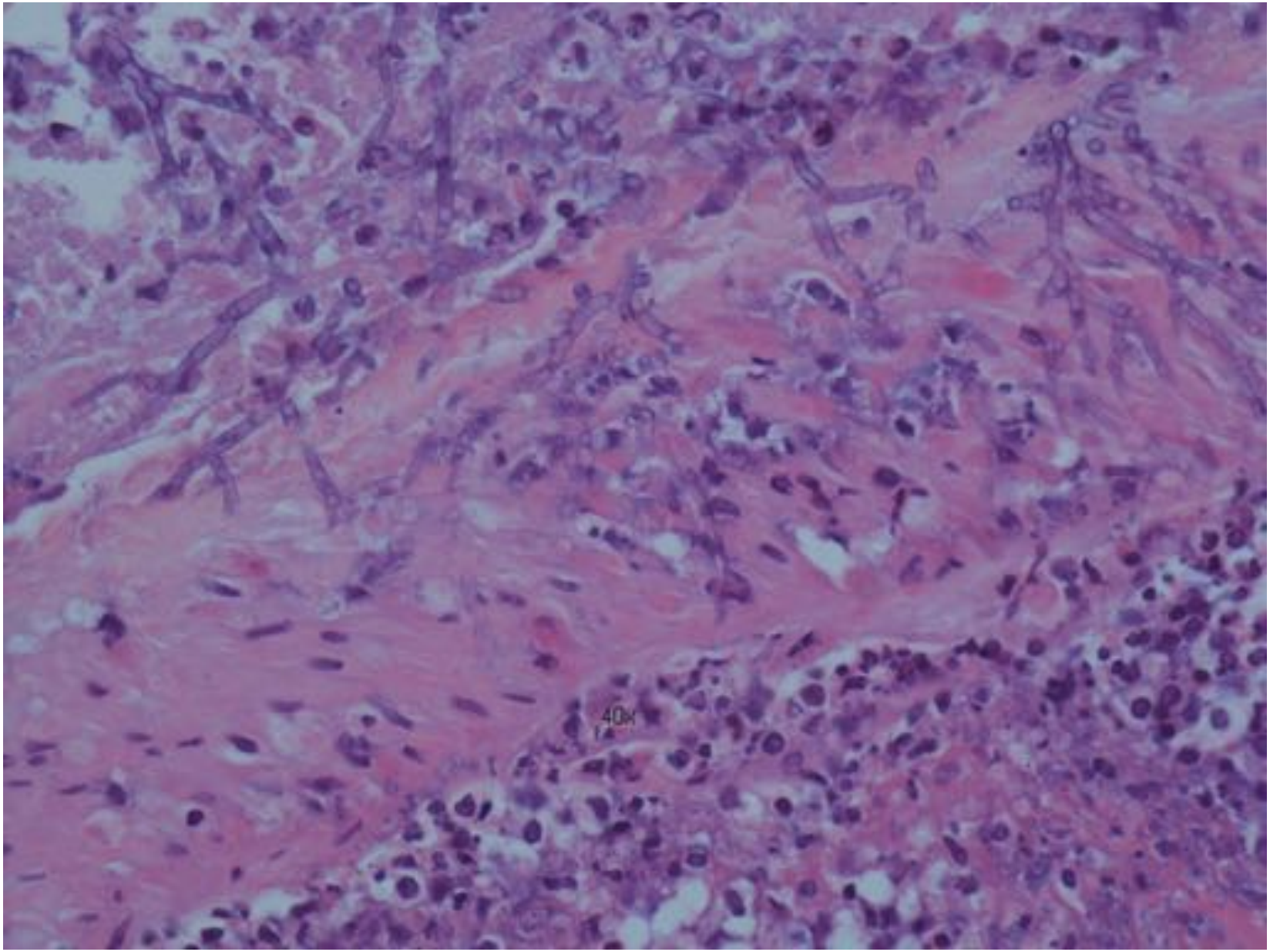

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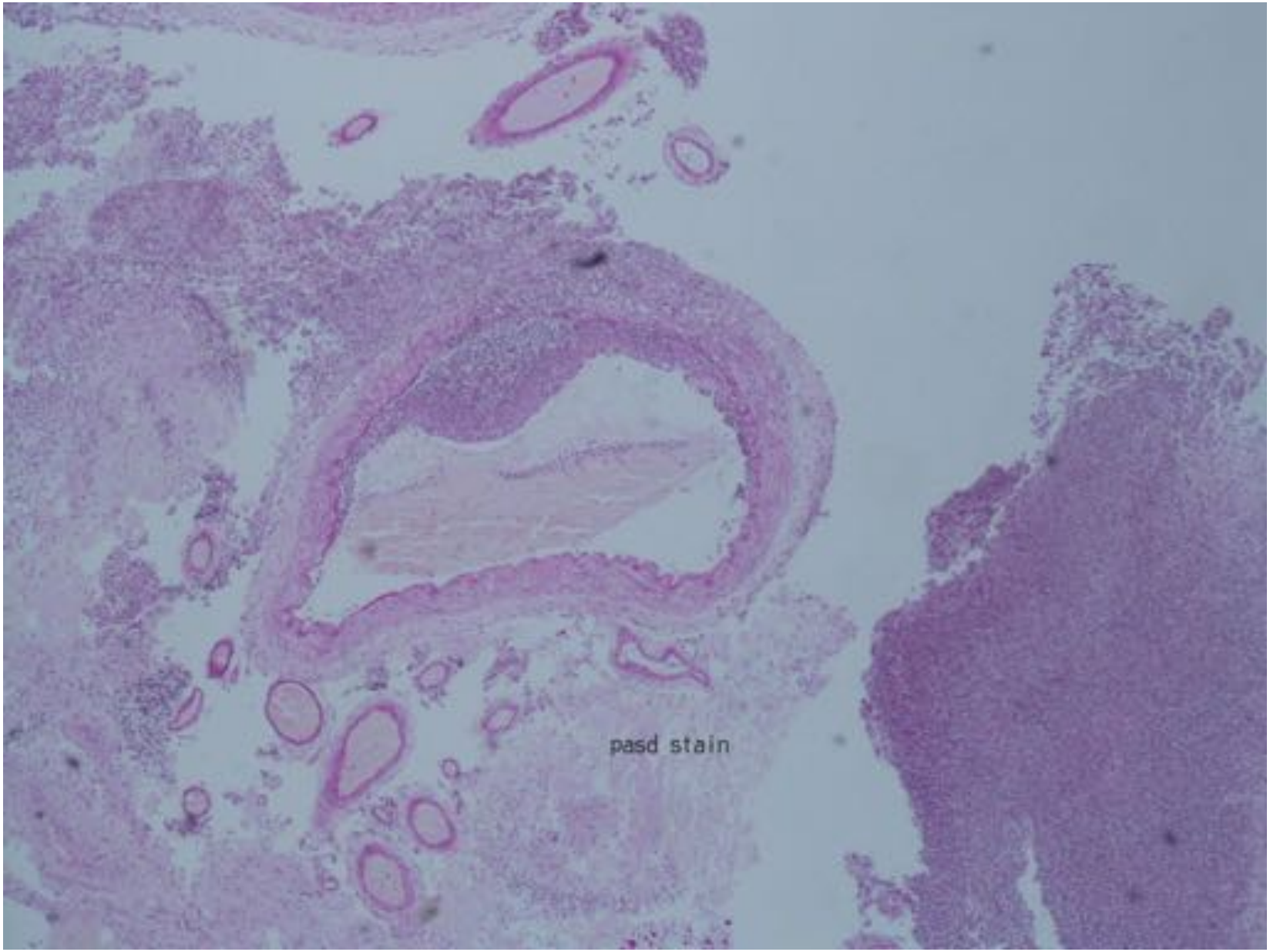

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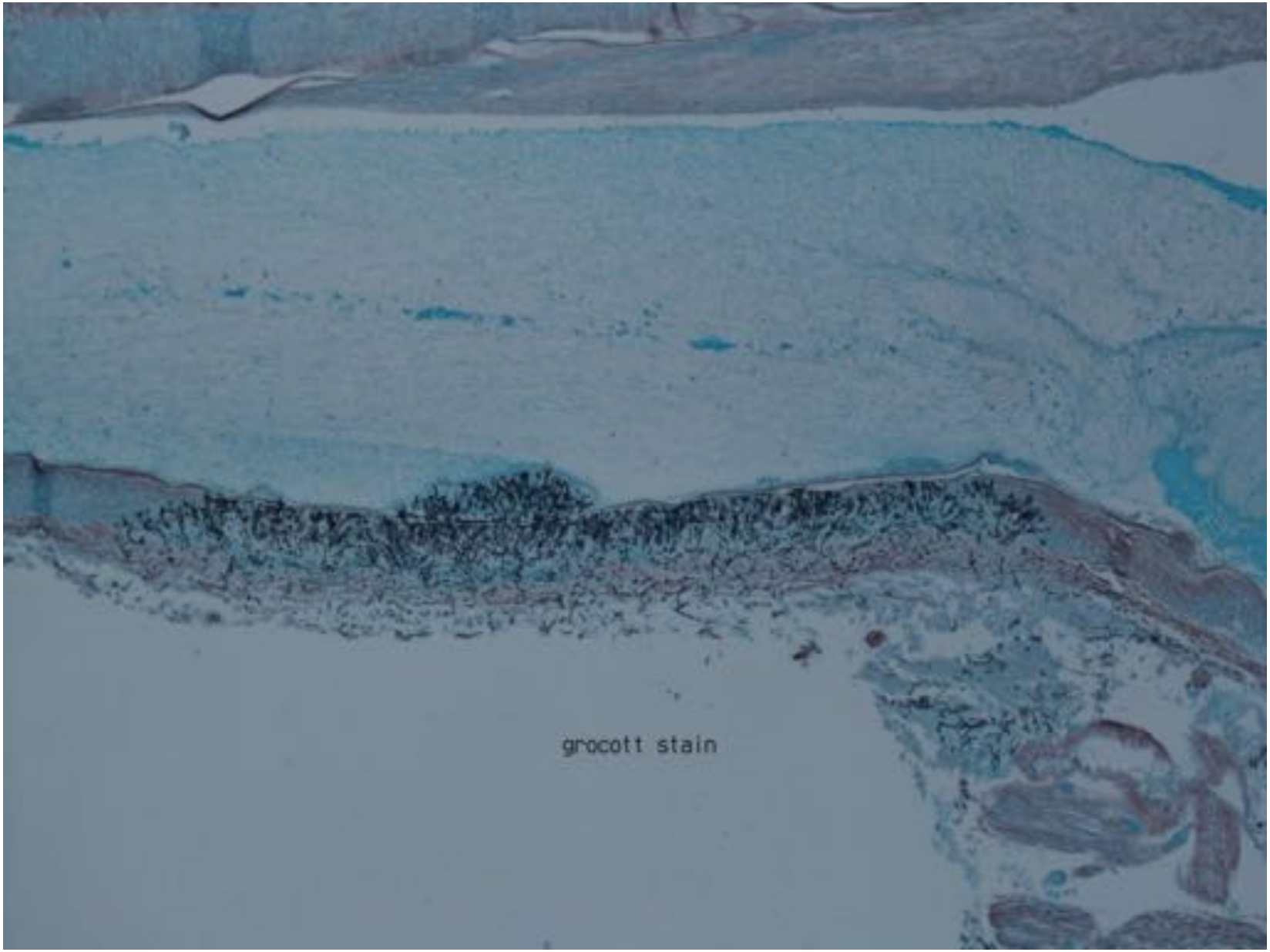

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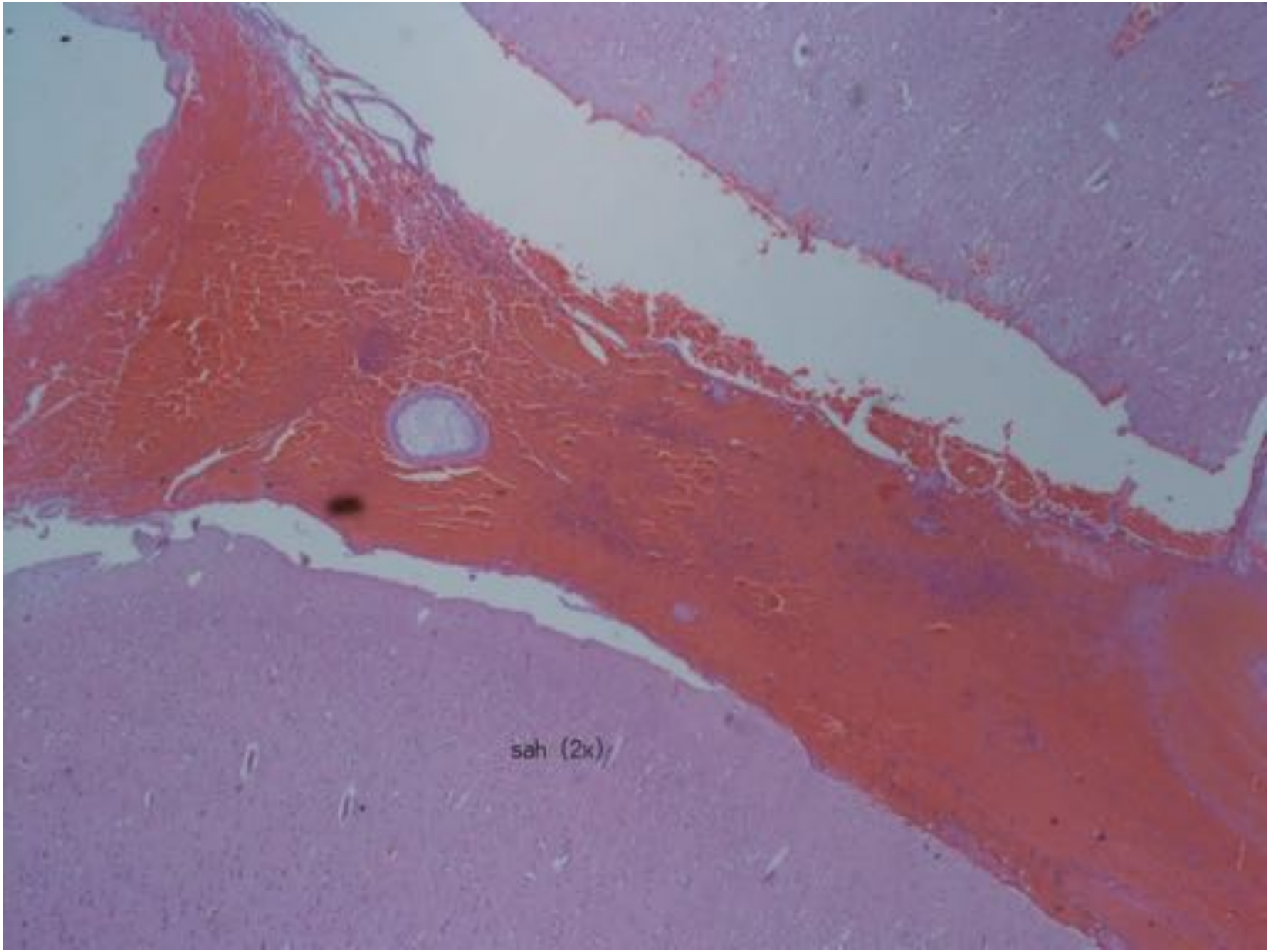

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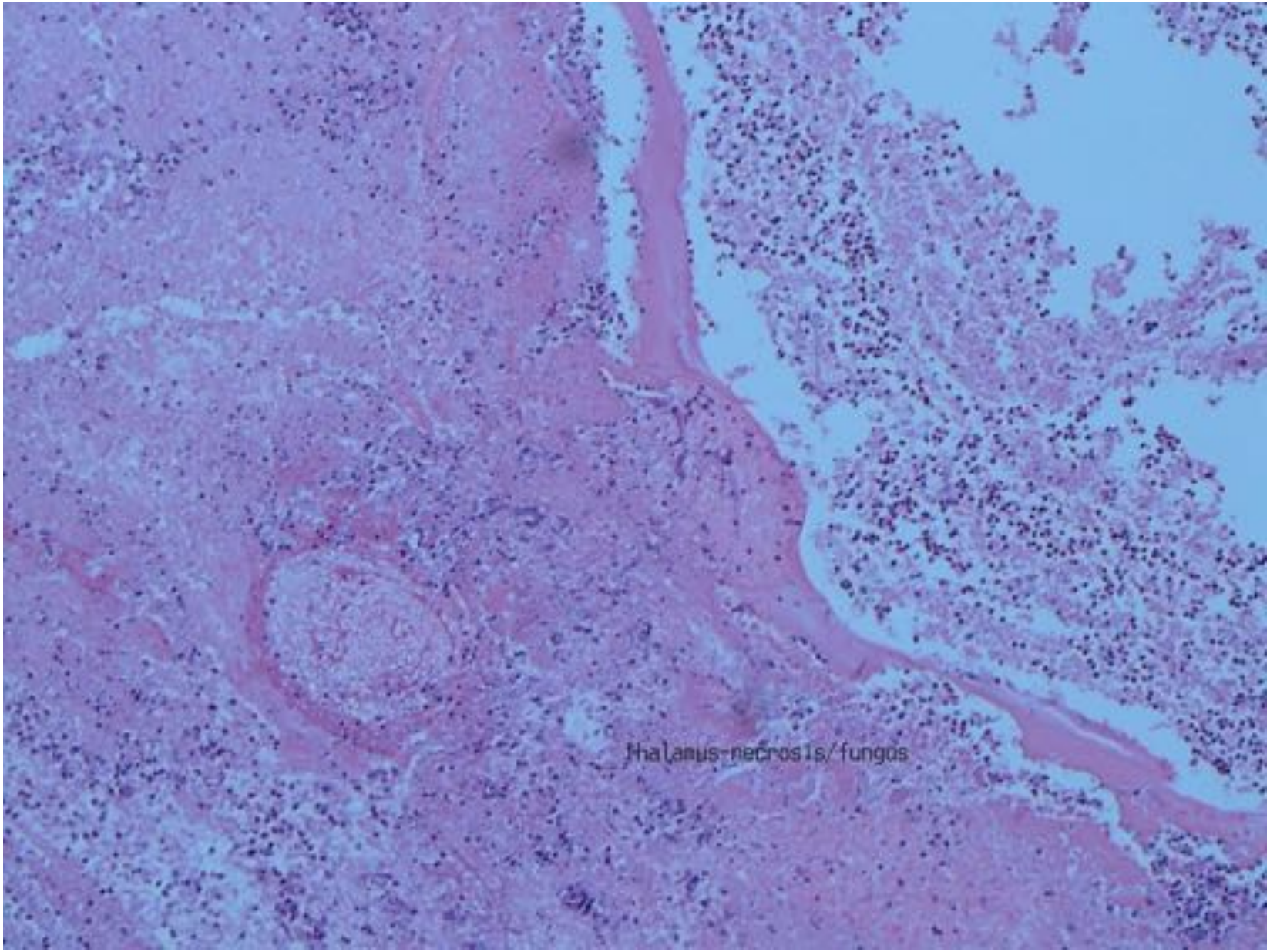

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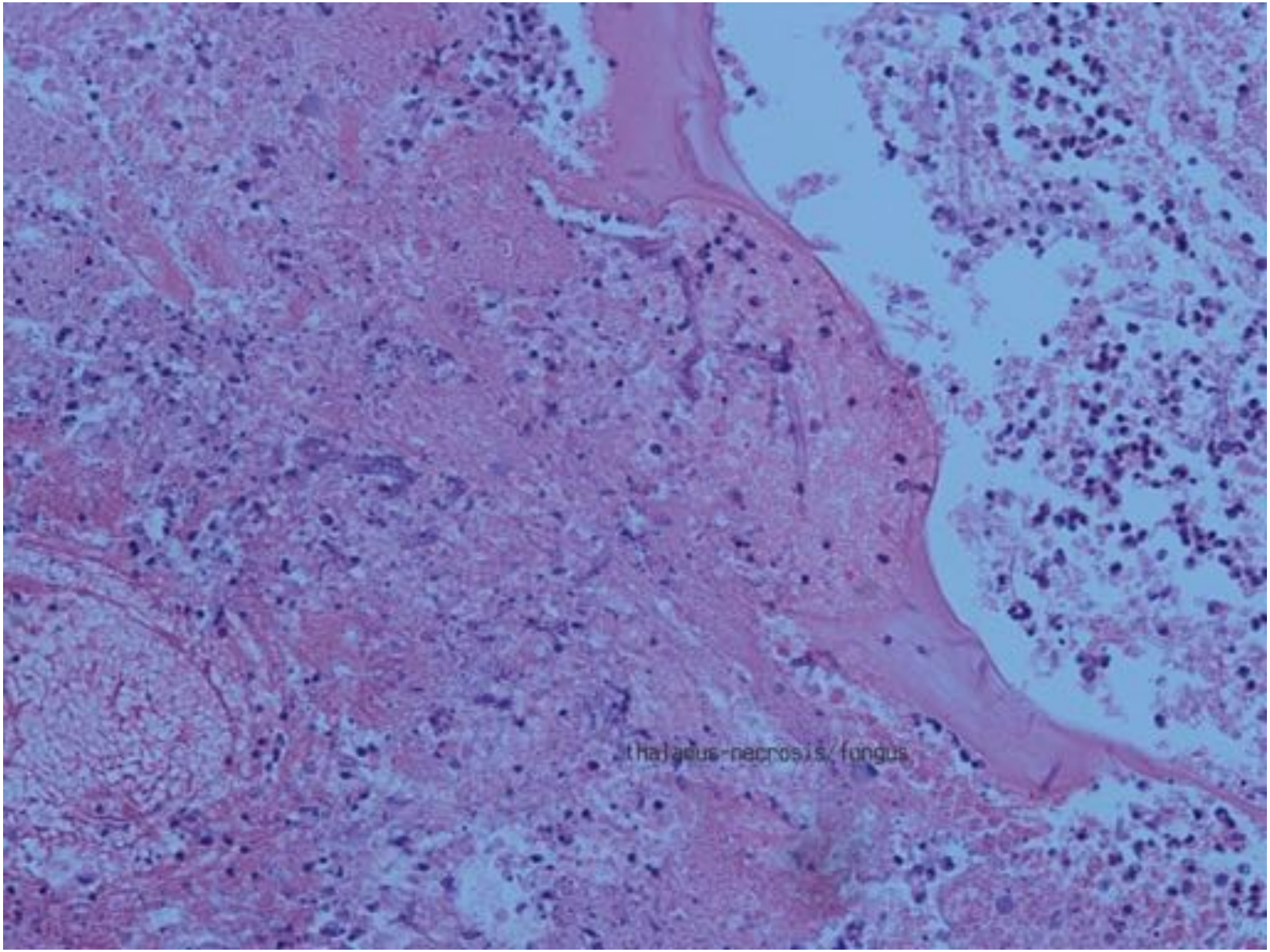

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Pathological diagnosis: (Aspergillus) Fungal encephalomeningitis

(Cerebral) Aspergillosis

Aspergillosis

- Aspergillosis is a spectrum of diseases of humans and animals caused bymembers of the genus Aspergillus.
- These include
- (1) **mycotoxicosis** due to ingestion of contaminated foods
- (2**) Allergy** and sequelae to the presence of conidia or transient growth of the organism in body orifices
- (3) **Colonization** without extension in preformed cavities and debilitated tissues
- (4) **Invasive**, inflammatory, granulomatous, necrotizing disease of lungs, and other organs
- (5) And rarely**, systemic and fatal disseminated disease**. The type of disease and severity depends upon the physiologic state of the host and the species of Aspergillus involved.

Aspergillosis

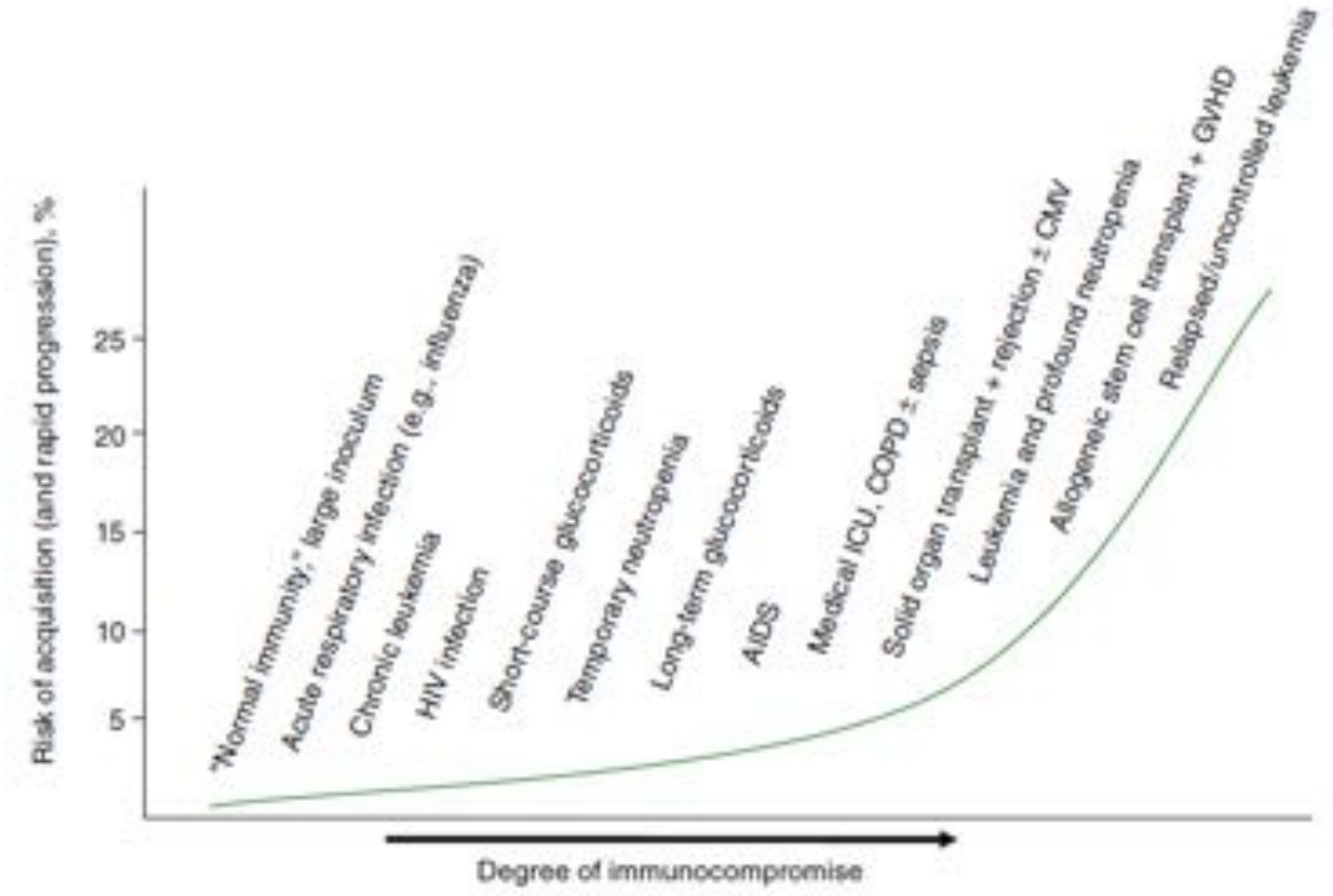
- Aspergillum: Latin aspergere, "to scatter"

- History:
  - 1729--Micheli noted pattern of conidial head of aspergillus with spore heads radiating from central structure resembling Aspergillum (perforated globe used to sprinkle holy water)
  - 1809--Link named Aspergillus flavus
  - 1842--John higes Bennett described Aspergillosis(in lung)
  - 1965—Raper & Fennel: 151 species, 18 groups.

Aspergillosis

- Mycology:
- Aspergillus spp are saprophytic moulds (decaying matter world wide)
- Out of 185 spp only 20 causes human disease
- 3 out of 20 are consistently & regularly encountered as etiological agent in 95% cases A.flavus, A.fumigatus, A.niger.
- Other common spp: A.terreus, A.glaucus,A.nidulans, A.oryzae & A.clavatus.

Mainly a disease of the immunocompromised



DL Kasper, AS Fauci. Harrison's Infectious Disease.

Spectrum of diseases

MAJOR MANIFESTATIONS OF ASPERGILLOSIS				
	MAJOR MANIFESTATIONS IN INDICATED TYPE OF DISEASE			
ORGAN	INVASIVE (Acute and subacute)	Chronic	Saprophytic	Allergic
Lung	Angioinvasive in neutropenia, non-angioinvasive, granulomatous	Chronic cavitatory, chronic fibrosing	Aspergilloma (single), airway colonization	Allergic bronchopulmonary severe asthma with fungal sensitization, extrinsic allergic alveolitis
Sinus	Acute invasive	Chronic invasive, chronic granulomatous	Maxillary fungal ball	Allergic fungal sinusitis, eosinophilic fungal rhinosinusitis
Brain	Abscess, haemorrhagic infarction, meningitis, mycotic cerebral aneurysm	Granulomatous, meningitis	None	None
Skin	Acute disseminated, locally invasive (trauma, burns, IV access)	External otitis, onychomycosis	None	None
Heart	Endocarditis (native or prosthetic), pericarditis	None	None	None
Eye	Keratitis, endopthalmitis (postoperative and disseminated)	None	None	None described

DL Kasper, AS Fauci. Harrison's Infectious Disease.

Similar clinical courses in the literature

Similar clinical courses

Korean J Ophthalmol
Vol. 16:119-123, 2002

Aspergillosis Presenting as an Optic Neuritis

Mi Young Choi, MD, Il Hun Bae, MD,*
Jong Hoon Lee, MD, Seong Jun Lee, MD**

*Department of Ophthalmology, *Department of Diagnostic Radiology,*
College of Medicine, Chungbuk National University & Chungbuk National University
Medical Research Institute, Cheongju,
***Department of Ophthalmology, College of Medicine, Dankook University, Chenan, Korea*

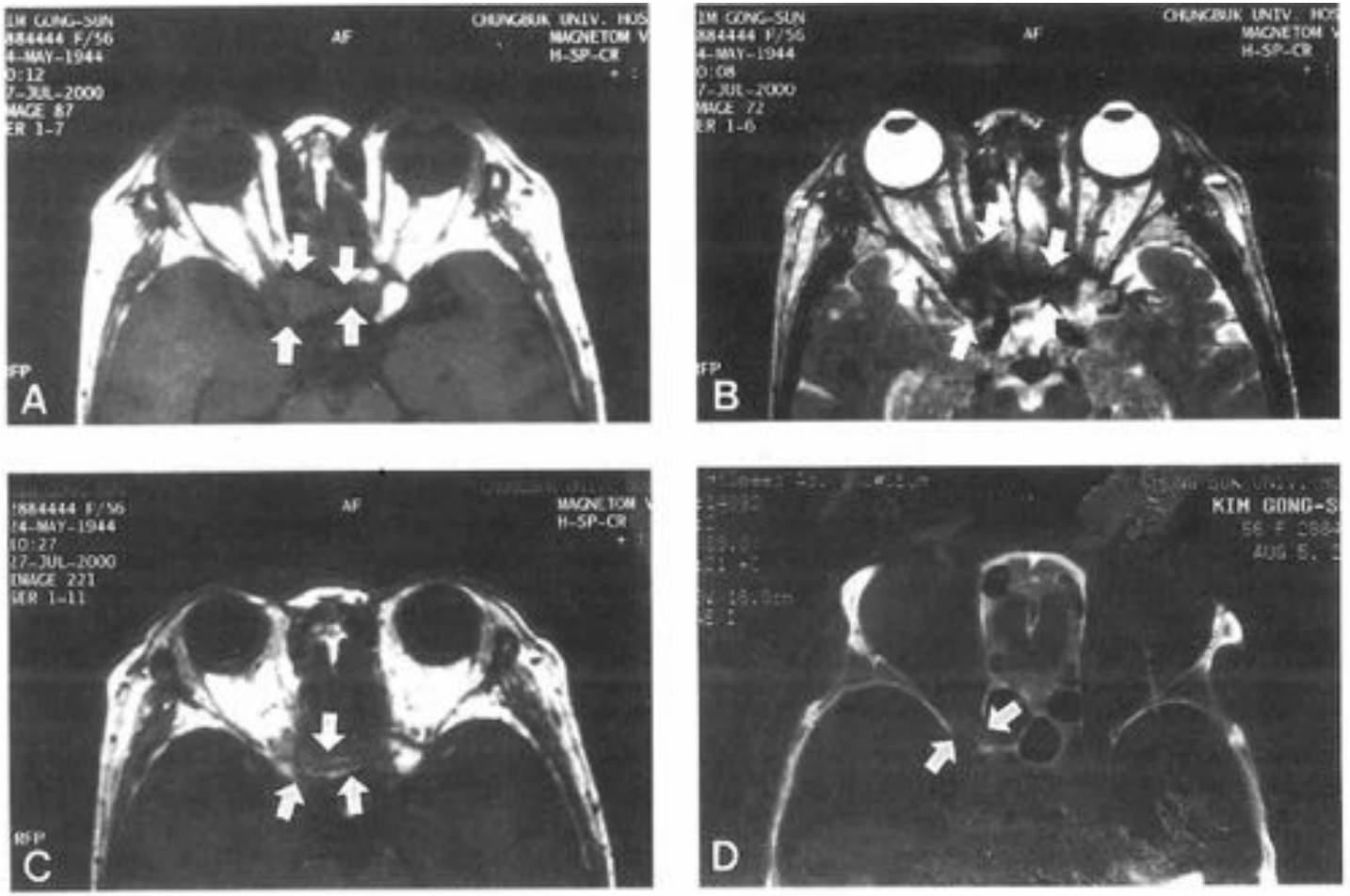
Similar clinical courses

- 59-year-old woman referred for blindness in right eye for 1 month. 2-month history of DM
- Visual acuity 20/50 in right, 20/20 in the left; Right RAPD.
- Fundoscopy: no blurring of optic disc.
- Visual evoked responses revealed delay on the right side
- CT showed no optic nerve or brain lesion.
- Started on 40mg per day oral prednisolone for 2 weeks.

- 2 months later developed right eye total blindness. Fundoscopy showed blurred optic discs on both sides.
- EOM exam found limitation in abduction and adduction.

Choi MY, Bae IH, Lee JH, Lee SJ. Aspergillosis presenting as an optic neuritis. Korean journal of ophthalmology : KJO. 2002;16(2):119-23.

Similar clinical courses



Choi MY, Bae IH, Lee JH, Lee SJ. Aspergillosis presenting as an optic neuritis. Korean journal of ophthalmology : KJO. 2002;16(2):119-23.

Similar clinical courses

J. Clin. Neuro-ophthalmol. 2: 103-107, 1982.

Aspergillosis Presenting as a Corticosteroid-Responsive Optic Neuropathy

THOMAS C. SPOOR, M.D.
WALTER C. HARTEL, M.D.
SALLY HARDING, M.D.
GARY KOCHER, M.D.

- 49-year-old lady diagnosed to have optic neuritis of left side
- Given steroid with complete resolution of visual symptoms, almost complete recovery of visual acuity
- Recurrent symptoms, resolved with repeated high dose steroid
- Developed right hemiplegia with LP found abnormal CSF with neutrophilia, but no growth
- Biopsy from nasopharyngeal sinus found aspergillosis

Spoor TC, Hartel WC, Harding S, Kocher G. Aspergillosis presenting as a corticosteroid-responsive optic neuropathy. Journal of clinical neuro-ophthalmology. 1982;2(2):103-7.

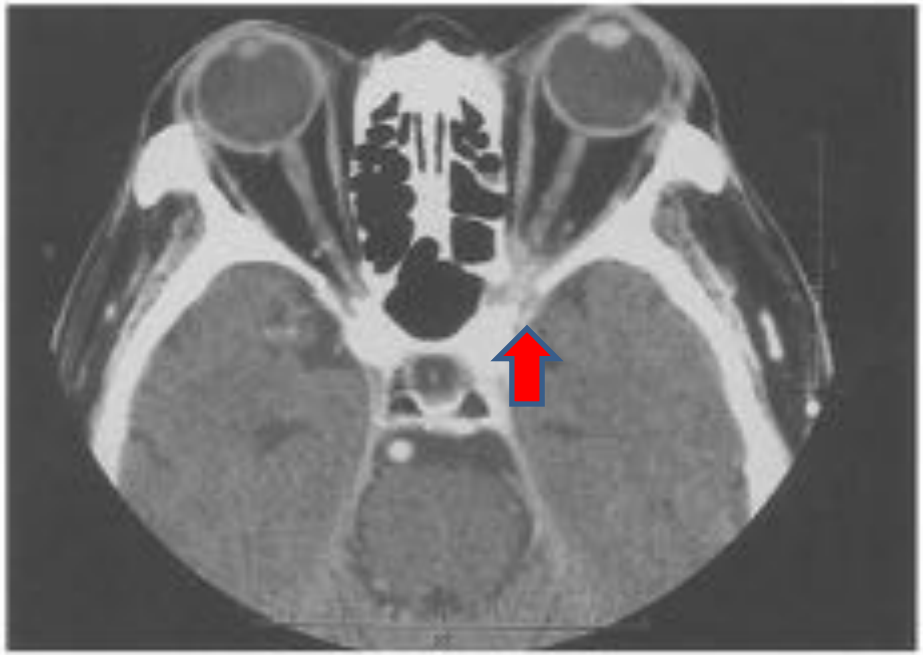
Similar clinical courses – in Hong Kong

Clinical Radiology (1998) **53**, 774–777

Case Report: 'Orbital Pseudo-pseudotumour' – a Fatal Case of Steroid-responsive Painful Ophthalmoplegia

P. S. F. LEE, W. MAK.*, P. IP† and R. J. COLLINS†

*Department of Diagnostic Radiology, Queen Mary Hospital, *Department of Medicine and †Pathology, University of Hong Kong, Hong Kong*



- 75-year-old diabetic man presented with left-sided temporal headache
- for 1 month. His left eye became red and painful with gradual deterioration of vision over 2 weeks
- CT brain found left orbital apex soft tissue mass, diagnosed as orbital pseudotomour given steroid
- Deteriorated with stroke and died
- Post-mortem found aspergillosis in the "pseudotumour"

Lee PS, Mak W, Ip P, Collins RJ. Case report: 'Orbital pseudo-pseudotumour'--a fatal case of steroid-responsive painful ophthalmoplegia. Clinical radiology. 1998;53(10):774-7.

Not much investigations done by Ophthalmologist at initial diagnosis ?

ONTT

The Clinical Profile of Optic Neuritis

Experience of the Optic Neuritis Treatment Trial

Optic Neuritis Study Group

The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Archives of ophthalmology. 1991;109(12):1673-8.

ONTT – Characteristic patient

- A young adult woman **with visual loss progressing over several days**, accompanied **by eye pain usually worsened by eye movement**, with the optic disc appearing either normal (64.7%) or swollen (35.3%).
- The degree of visual loss varied considerably from a **mild visual field defect with normal visual acuity to no light perception**. The distributions of patient characteristics

The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Archives of ophthalmology. 1991;109(12):1673-8.

ONTT

- No patient with positive findings on the ANA test had a history suggestive of collagen vascular disease.
- In 11 of the 15 patients with an ANA titer 1:320 or greater, additional rheumatologic evaluations (such as anti-cardiolipin antigen, latex fixation, and complement studies) were performed and the results were unremarkable.
- One patient subsequently developed arthritis and was diagnosed as having a connective tissue disease.

ANA titer	No. (%)
0	374 (83.7)
<1:320	58 (12.9)
>1:320	15 (3.4)

Limited value to screen for connective tissue disease

The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Archives of ophthalmology. 1991;109(12):1673-8.

ONTT

- The **CXR** was unremarkable in all patients. In particular, there was no evidence of sarcoidosis in any patient.
- **Lumbar puncture** was performed in only 31.5% of patients, in no case did the results suggest an etiologic factor for the optic neuritis other than demyelination.
- The **FTA-ABS titer** was positive in six of the 448 patients. No patients were thought to have active syphilis as the cause of the optic neuritis.

The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Archives of ophthalmology. 1991;109(12):1673-8.

ONTT - MRI

Development of Multiple Sclerosis according to number of baseline Brain Magnetic Resonance Imaging (MRI) Lesions				
No. of Brain MRI Lesions at Study Enrollment	No. of Patients	10-y Risk of Multiple Sclerosis, %		Hazard Ratio (95% Confidence interval)
0	191	22		1.0
1	44	51		2.77 (1.64-4.67)
2-4	51	50		2.97 (1.80-4.92)
5-8	37	70		4.90 (2.98-8.06)
>=9	28	57		3.94 (2.19-7.06)
Total	388	38		

MRI for brain lesion is more of prognostic implication, whether patient is likely to developed multiple sclerosis

Beck RW, Trobe JD, Moke PS, Gal RL, Xing D, Bhatti MT, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. Archives of ophthalmology. 2003;121(7):944-9.

ONTT

- Optic neuritis remains a disorder that is diagnosed on **clinical grounds**.
- Laboratory and radiological studies may be supportive but are not diagnostic. The clinician must define appropriate work-up to exclude treatable causes of optic neuritis and to discover other causes of optic neuropathies. In the patient with a typical course and clinical findings of acute optic neuritis, with no historical features or examination findings to suggest a non-demyelinative cause for the optic neuropathy, the clinician can have a high degree of assurance that the diagnosis is correct, **without ancillary studies**.

The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Archives of ophthalmology. 1991;109(12):1673-8.

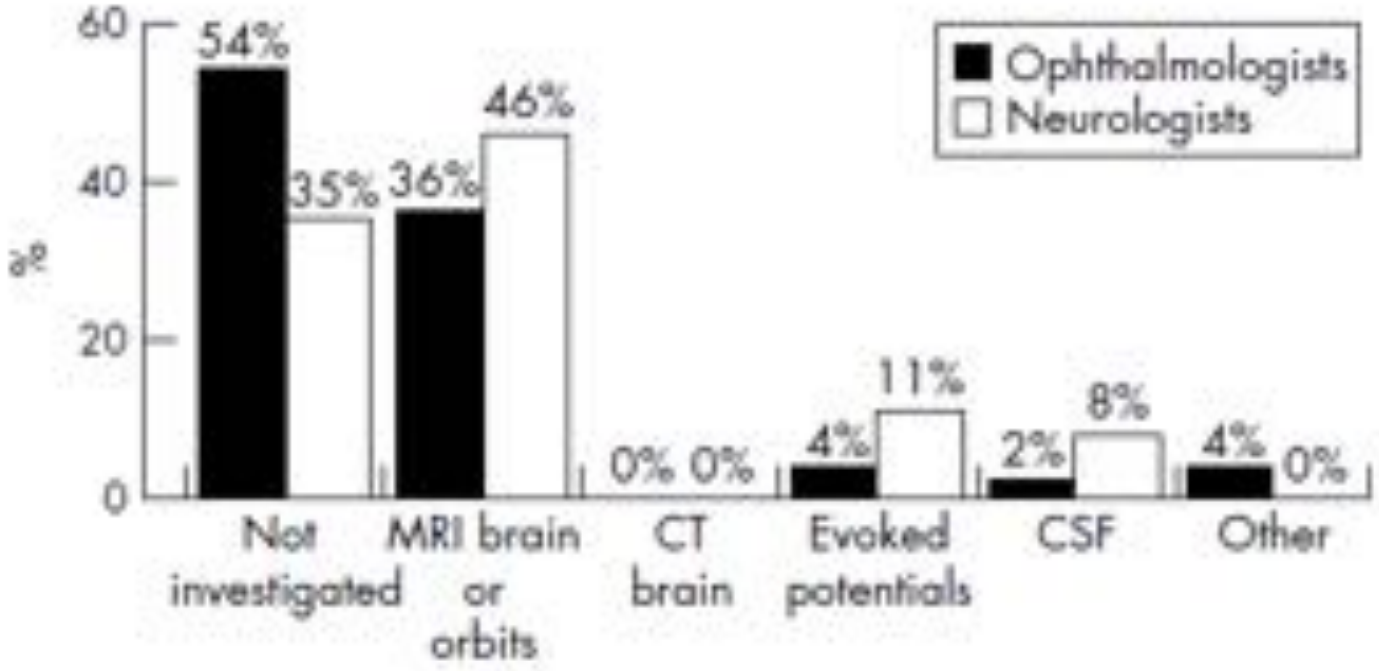
Very long list of suggested investigations by Neurologists

CSF features atypical for multiple sclerosis at initial presentation
White blood cells >50, protein >80 mg/dl, absence of oligoclonal bands (by isoelectric focusing technique).

- CNS *inflammatory/autoimmune disease*: ANA (Antinuclear Antibody), ESR (Erythrocyte Sedimentation Sate), ACE (Angiotensin-Converting Enzyme), CRP (C-reactive protein), anti-dsDNA, C3, C4, ANCA (Anti-neutrophil Cytoplasmic Antibody) panel, anti-aquaporin-4 antibodies, chest CT (computed tomography), eye exam, conjunctival biopsy, gallium scan, pathergy skin test (Behçet's), skin biopsy if suspicious rash present, CTA (Computed Tomography Angiography), angiogram.
- CNS *infection*[11]: Brucella titer, Borrelia titer, CSF, VDRL (Venereal disease research laboratory test), HIV test, HTLV1 (Human T-lymphotropic Virus Type I), Toxocara canis serum and CSF antibodies (if isolated myelopathy with a lesion on spinal MRI), ESR, CSF JC (John Cunningham) virus PCR (Polymerase Chain Reaction), serum and CSF Whipple PCR, small bowel biopsy for Whipple.
- CNS *neoplasm/infiltrative disorder*: CSF cytology and flow cytometry, CXR (Chest X-ray), CT chest/abdomen/pelvis, pelvic ultrasound, mammogram, LDH (Lactate Dehydrogenase), PET (Positron Emission Tomography) scan, skeletal series, bone scan, brain biopsy.
- CNS *vasculopathy/ischemic disease*: Anticardiolipin antibodies, Notch3 mutations in CADASIL, MRA (Magnetic Resonance Angiography), CTA, standard angiogram, thrombophilia panel, lupus anticoagulant.
- *Nutritional deficiency/toxicity*: Vitamin B12, copper, zinc, ceruloplasmin, folate, heavy metal screen.
- *Dysmyelinating/metabolic disorders*[12]: Lumbar puncture, EMG/NCVs (Electromyography/Nerve Condition Velocitlies), biochemical studies, buccal or rectal mucosa biopsy for electron microscopy if neuronal ceroid lipofuscinosis (NCL) suspected, skin biopsy for fibroblast cultures (enzyme assays), or peripheral blood smear (vacuolated monocytes in NCL), brain biopsy (rarely needed), fingerprint profiles, curvilinear and rectilinear bodies by E.M. (Electron Microscopy) in NCL oligodendrocytes, diffuse white matter gliosis by light microscopy in NCL.
- *Urine/blood for biochemical studies:* including levels of WBC (White Blood Cells) arylsulfatase A, very long chain fatty, fasting arterial lactate, quantitative plasma amino acid and urine organic acid analyses, hexosaminidase A, galactocerebrosidase C (Gal-C), palmitoyl protein thioesterase 1 (adults), tripeptidyl peptidase 1, CLN3, and CLN5, NPC-1 (Niemann Pick).

Yamout B, Alroughani R, Al-Jumah M, Khoury S, Abouzeid N, Dahdaleh M, et al. Consensus guidelines for the diagnosis and treatment of multiple sclerosis. Current medical research and opinion. 2013;29(6):611-21.

Different approaches by ophthalmologist and neurologists



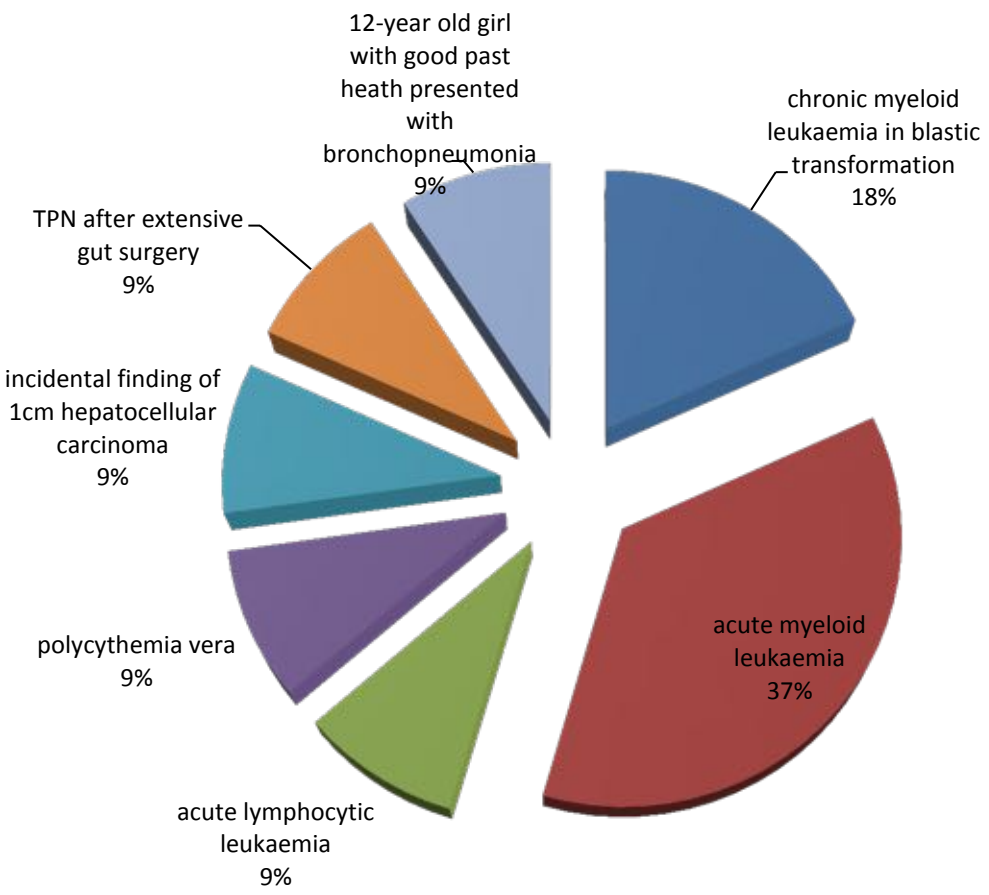
Ghosh A, Kelly SP, Mathews J, Cooper PN, Macdermott N. Evaluation of the management of optic neuritis: audit on the neurological and ophthalmological practice in the north west of England. Journal of neurology, neurosurgery, and psychiatry. 2002;72(1):119-21.

Differential diagnosis

- *Unilateral ON*
  - Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)
  - Infectious/ inflammatory
    - Neuroretinitis
    - Viral
    - Post- viral
    - Fungal
    - Syphilis
    - Toxoplasmosis
    - Lyme
    - Herpes zoster
    - Sarcoidosis
    - T.B.
    - Collagen vascular disease
    - Autoimmune ON
  - Leber's hereditary ON
  - Compressive
    - Meningioma
    - Glioma
    - Metastasis
    - PNS mass
  - Infiltrative
    - Multiple myeloma
    - Leukemia
  - Retinopathies
    - Paraneoplastic ON
    - Cone dystrophy

Local Data of Aspergillosis

Local data of Invasive Aspergillosis



- All cases have infection in lungs
- the sites include the liver, spleen, kidneys and the heart
- Invasive aspergillosis was not diagnosed until necropsy in all our 11 cases
- Repeated cultures for aspergillus were negative and trans-bronchial biopsy specimens were taken in the three cases, but none was considered diagnostic of aspergillosis.

Total cases = 11

1987 – 1990 in QMH identified from autopsies

Shek WH, Chan KL, Luk IS. Experience of invasive aspergillosis in Hong Kong. Journal of clinical pathology. 1992;45(2):183.

Case report in Hong Kong

High dose ketoconazole in the treatment of cerebral aspergilloma

Y.L. Kwong*, Y.L. Yu*, F.L. Chan* *, K.S.L. Lam*, E. Woo*, and C.Y. Huang*

- A 32-year-old housewife with lupus nephritis on steroid and azathioprine presented with severe headache and examination revealed bilateral papilloedema and right homonymous hemianopia.
- CT showed a contrast-enhanced loculated lesion in the left occipital lobe with surrounding oedema and mass effect treated with craniectomy, biopsy found aspergillosis
- Treated with Amphotericin B, without improvement until added on ketoconazole

Case series from Beijing

Table 3. Patients' clinical characteristics.

Case	Imaging features	Pathological findings/ Fungal culture	Surgery	Treatment	Outcome	Sequelae
1	Left cavernous sinus with long T1 and equal T2 signal	Granulomatous inflammation; PAS(+); *Aspergillus* hyphae	N	Voriconazole	Survived	
2	Occupied lesion in left cerebellum (from other institution)	Fungal culture: *Aspergillus;* Inflammatory granulation tissue with focal necrosis	Y	Fluconazole; itraconazole	Died	
3	Left frontal lobe, left sphenoid sinus and anterior skull base with multiple long T1 and long T2 signal; DWI: abnormal hyperintensity within central area of lesion; Enhancement Scan: ring-enhanced	*Aspergillus* hyphae	N	Voriconazole	Died	
4	Occupied lesion in cavernous sinus, hemorrhage signal in lesion	Inflammatory cell infiltration; PAS(+); *Aspergillus* hyphae	Y	Voriconazole; fluconazole	Survived	

Wang RX, Zhang JT, Chen Y, Huang XS, Jia WQ, Yu SY. Cerebral aspergillosis: a retrospective analysis of eight cases. The International journal of neuroscience. 2016:1-5.

Case series from Beijing

Table 3. Patients' clinical characteristics.

Case	Imaging features	Pathological findings/ Fungal culture	Surgery	Treatment	Outcome	Sequelae
5	Roundish lesion in right temporal lobe with long T1 and short T2 signal; DWI: hypointense; Enhancement Scan: ring-enhanced	*Aspergillus* hyphae	Y	Voriconazole	Survived	Hearing loss
6	Abnormal signal in right cavernous sinus, short T1 and short T2 signal; DWI: hyperintensity; Enhancement Scan: inhomogeneous enhancement; leptomeningeal enhancement; hydrocephalus	*Aspergillus* (autopsy)	N	Voriconazole; amphotericin B deoxycholate; fluorocytosine	Died	
7	abnormal signal in cavernous sinus and left optic canal, enhanced		N	Fluconazole, voriconazole	Died	
8	Cavernous sinus thickened, the right side significant, short T1 and equal T2 signal; DWI: hyperintensity; endocranium enhancement		N	Fluconazole	Died	

Wang RX, Zhang JT, Chen Y, Huang XS, Jia WQ, Yu SY. Cerebral aspergillosis: a retrospective analysis of eight cases. The International journal of neuroscience. 2016:1-5.

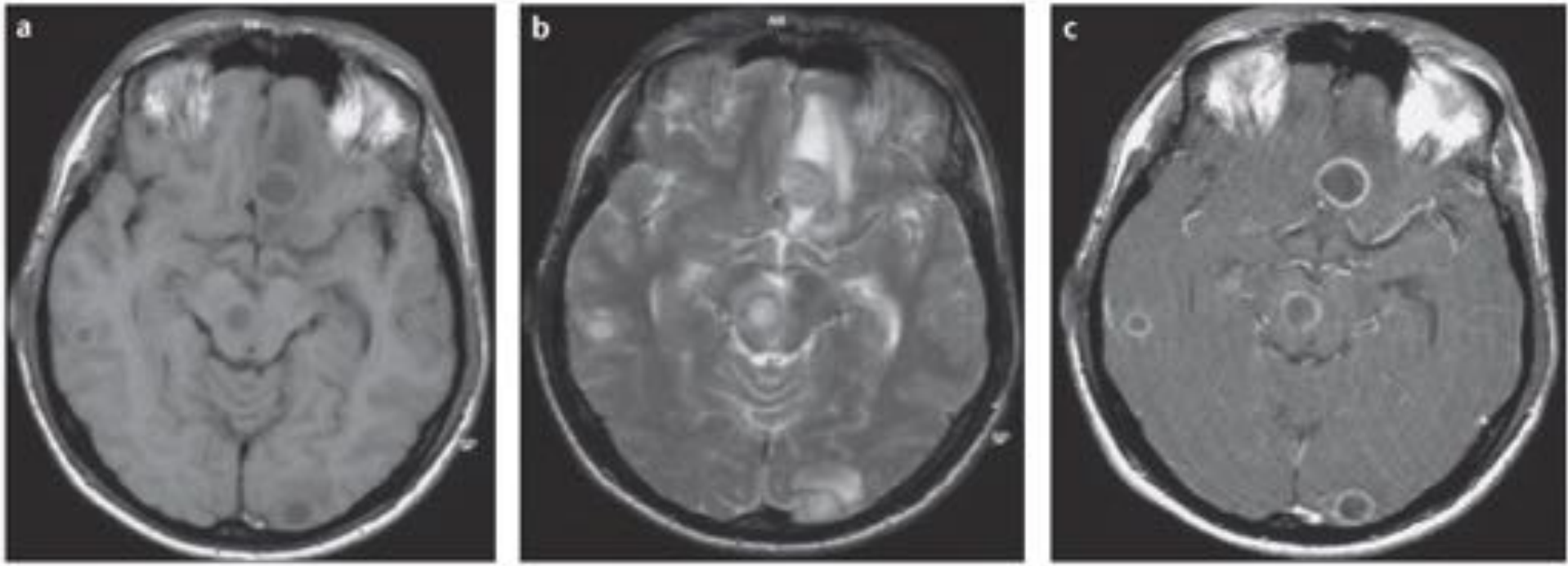
Radiological findings

Radiological findings

- Meningitis
- Abscess
- Mass lesions (granulomas, or thrombosis, infarction, hemorrhage)
- Mycotic aneurysm caused by vascular invasion

Keyik B, Edguer T, Hekimoglu B. Conventional and diffusion-weighted MR imaging of cerebral aspergillosis. Diagnostic and interventional radiology. 2005;11(4):199-201.

1. Abscess formation



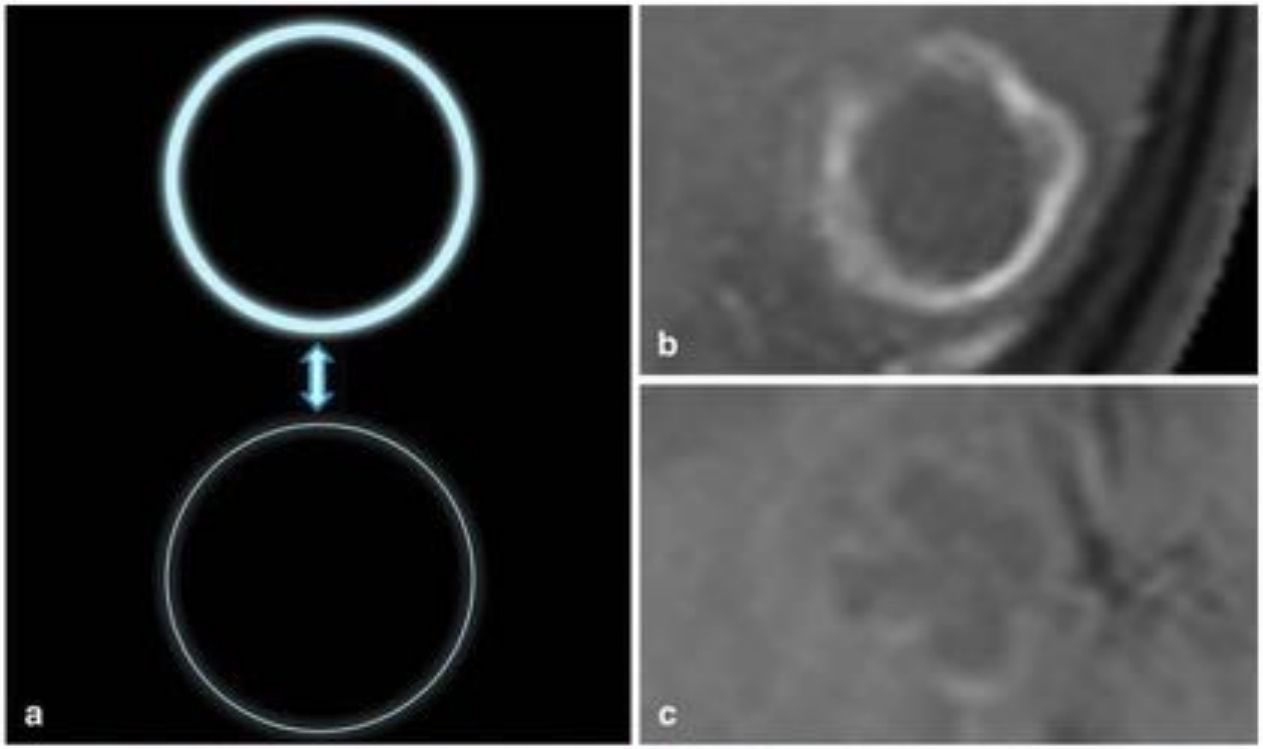
Weak rim enhancement also seen in mycetomas, pyogenic abscesses, metastatic lesions, and subacute hematomas.

Keyik B, Edguer T, Hekimoglu B. Conventional and diffusion-weighted MR imaging of cerebral aspergillosis. Diagnostic and interventional radiology. 2005;11(4):199-201.

Compared with bacterial abscess

– Thinner ring in fungal abscess

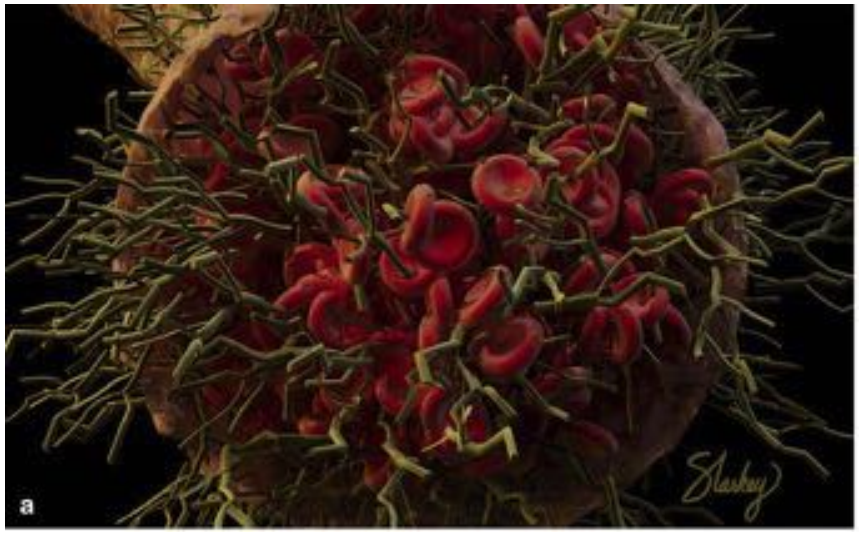
"Weak ring" enhancement in fungal infection may be explained by the relative lack of inflammatory response.



Starkey J, Moritani T, Kirby P. MRI of CNS fungal infections: review of aspergillosis to histoplasmosis and everything in between. Clin Neuroradiol. 2014;24(3):217-30.

2. Infarction & Micro-haemorrhage

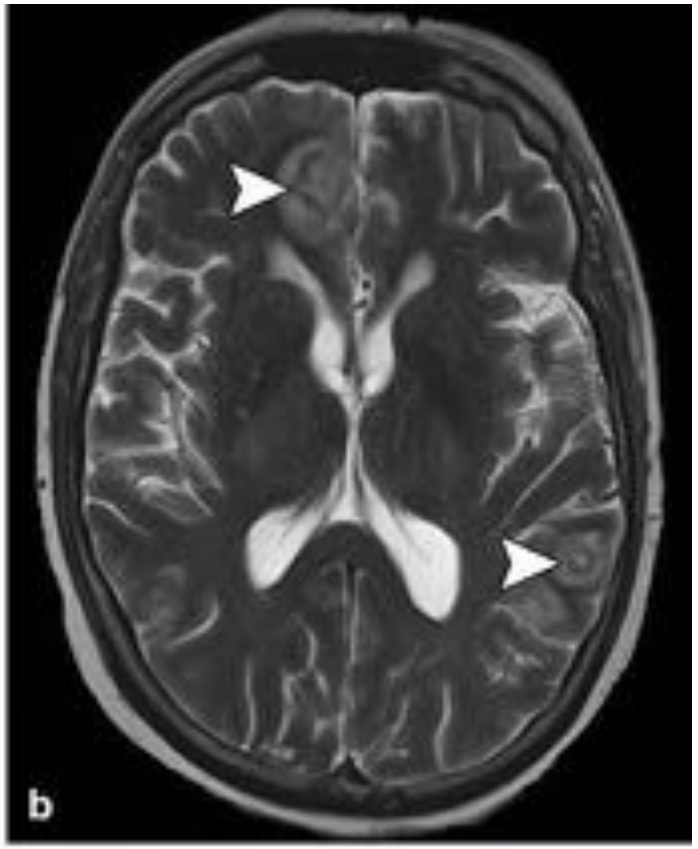
- Main feature in our case
- *Aspergillus* species are often angioinvasive, multiplying within blood vessels and producing artery-destroying elastases with resultant microhemorrhage and infection of adjacent brain parenchyma.
- Fungal elements also clog vessels and cause downstream sterile infarction.



Starkey J, Moritani T, Kirby P. MRI of CNS fungal infections: review of aspergillosis to histoplasmosis and everything in between. Clin Neuroradiol. 2014;24(3):217-30.

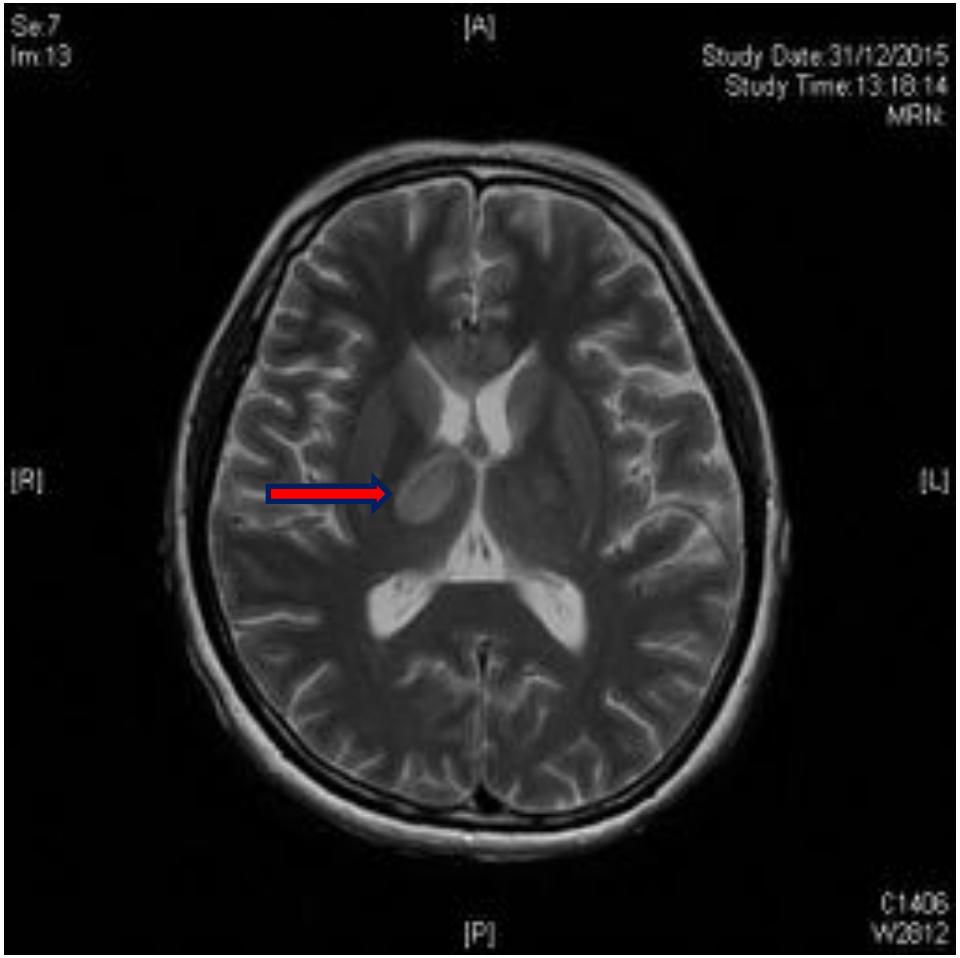
2. Infarction & Micro-haemorrhage

- Characteristic peripheral low intensity (*arrowheads),* which may be due to hemorrhage and increased iron due to fungal elements and hemorrhage.



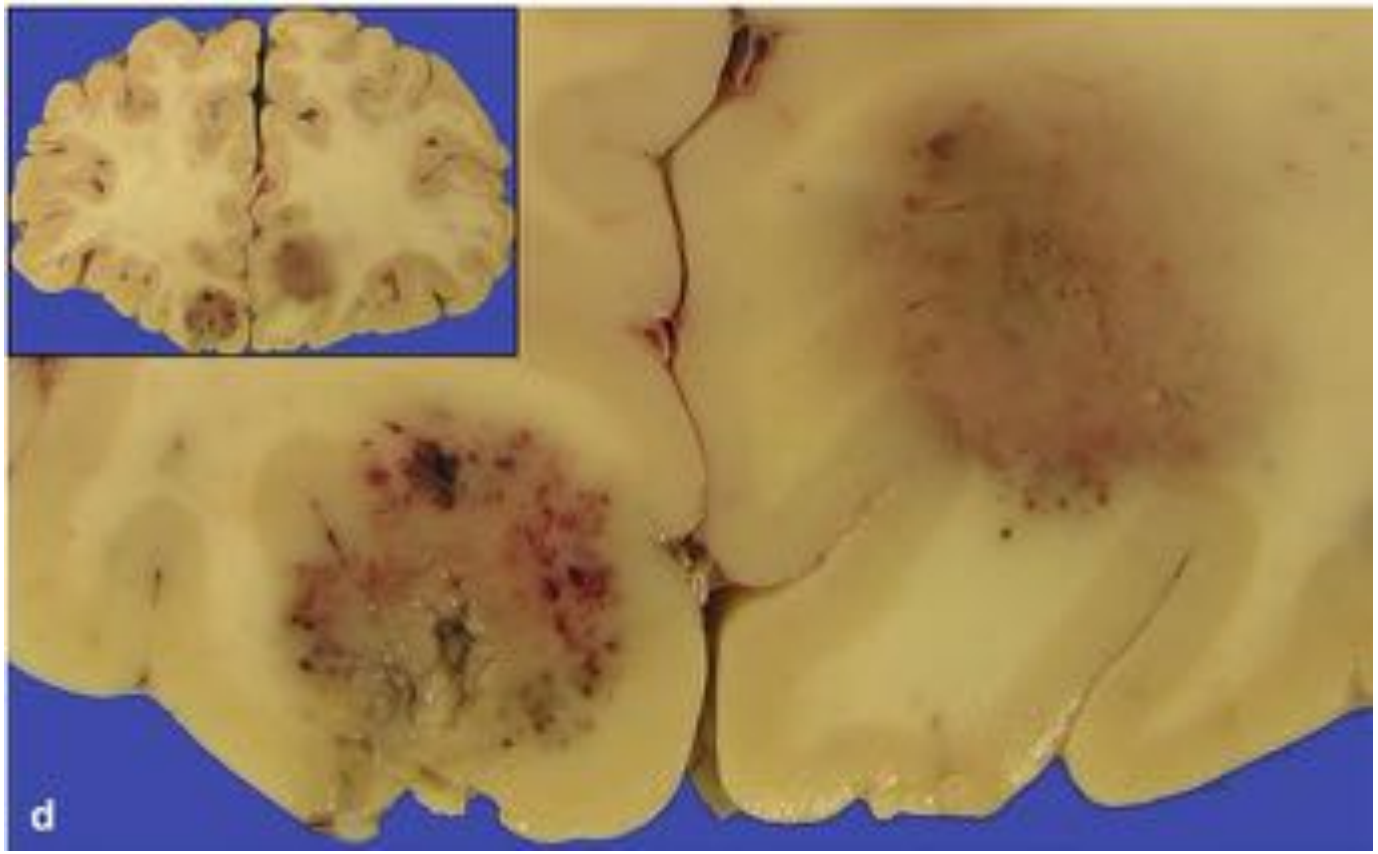
Starkey J, Moritani T, Kirby P. MRI of CNS fungal infections: review of aspergillosis to histoplasmosis and everything in between. Clin Neuroradiol. 2014;24(3):217-30.

Compatible with our case image



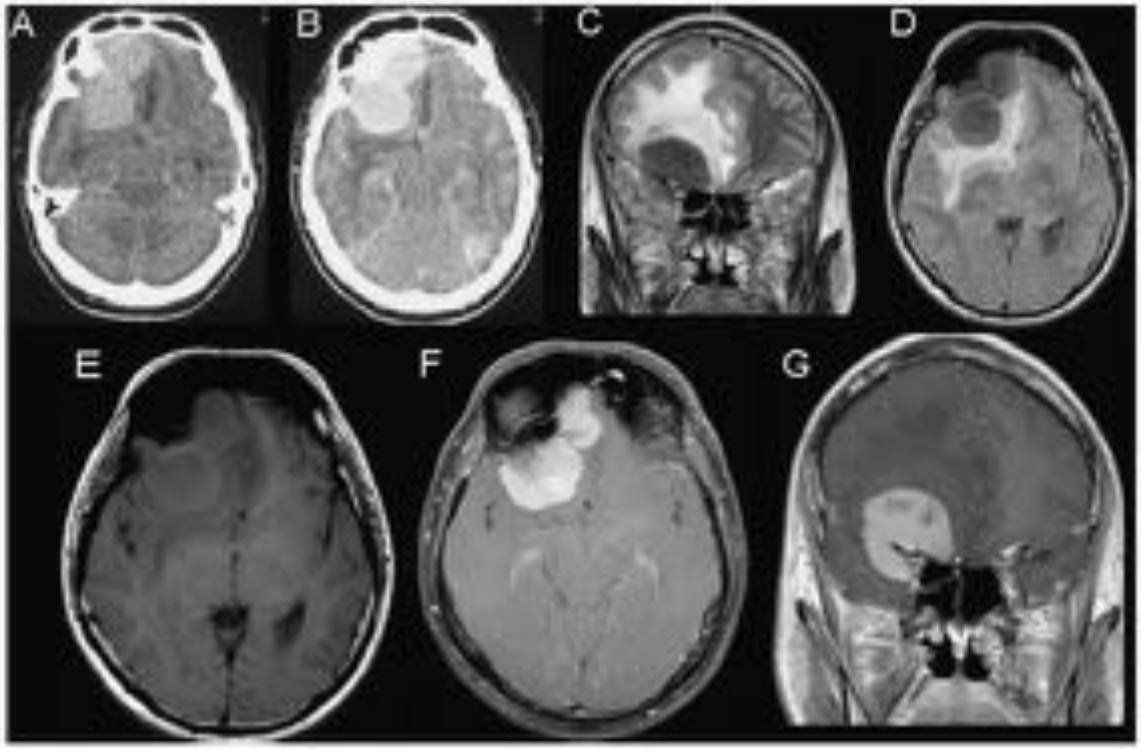
2. Infarction & Micro-haemorrhage

On gross examination - peripheral hemorrhage and central necrosis



Starkey J, Moritani T, Kirby P. MRI of CNS fungal infections: review of aspergillosis to histoplasmosis and everything in between. Clin Neuroradiol. 2014;24(3):217-30.

3. Granuloma



Banuprakash S, Jolappara M, Kesavadas C, Saini J, Rao RM, Radhakrishnan VV. Atypical fungal granuloma of the sphenoid wing. Journal of neuroradiology Journal de neuroradiologie. 2009;36(4):233-6.

Laboratory diagnosis of cerebral aspergillosis

Laboratory diagnosis

- Histology
- Culture
- **Serum galactomann**
- **Non-serum galactomann**

Recommendations by Case series from Beijing

- Use of local tissue puncture, surgery or other invasive means to obtain diseased tissue containing higher levels of *Aspergillus,* followed by culture or histological examination, can contribute to an early diagnosis of CA and timely therapeutic intervention.
- But not useful in patients who are already critically ill

Wang RX, Zhang JT, Chen Y, Huang XS, Jia WQ, Yu SY. Cerebral aspergillosis: a retrospective analysis of eight cases. The International journal of neuroscience. 2016:1-5.

Serum galactomannan

TABLE 3. ELISA results in 71 pathology-controlled cases

ELISA result	No. of patients		
	Invasive aspergillosis (n = 27)	No invasive aspergillosis (n = 44)	Total
Positive	25	2	27
Negative	2	42	44
Total	27	44	71

- Aspergillus-antigen test had a **sensitivity of 92.6% and specificity of 95.4%.**
- Examination of the temporal sequence of antigenaemia showed that the antigen was detectable in 65% of cases before the first clinical feature (eg, cough, chest pain, haemoptysis)
- In 71% before any lesion was apparent on the chest radiograph, in 44% before fever occurred, and in 72% before empirical antifungal therapy was given

Maertens J, Verhaegen J, Demuynck H, Brock P, Verhoef G, Vandenberghe P, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive Aspergillosis. Journal of clinical microbiology. 1999;37(10):3223-8.

Galactomannan level as disease monitoring

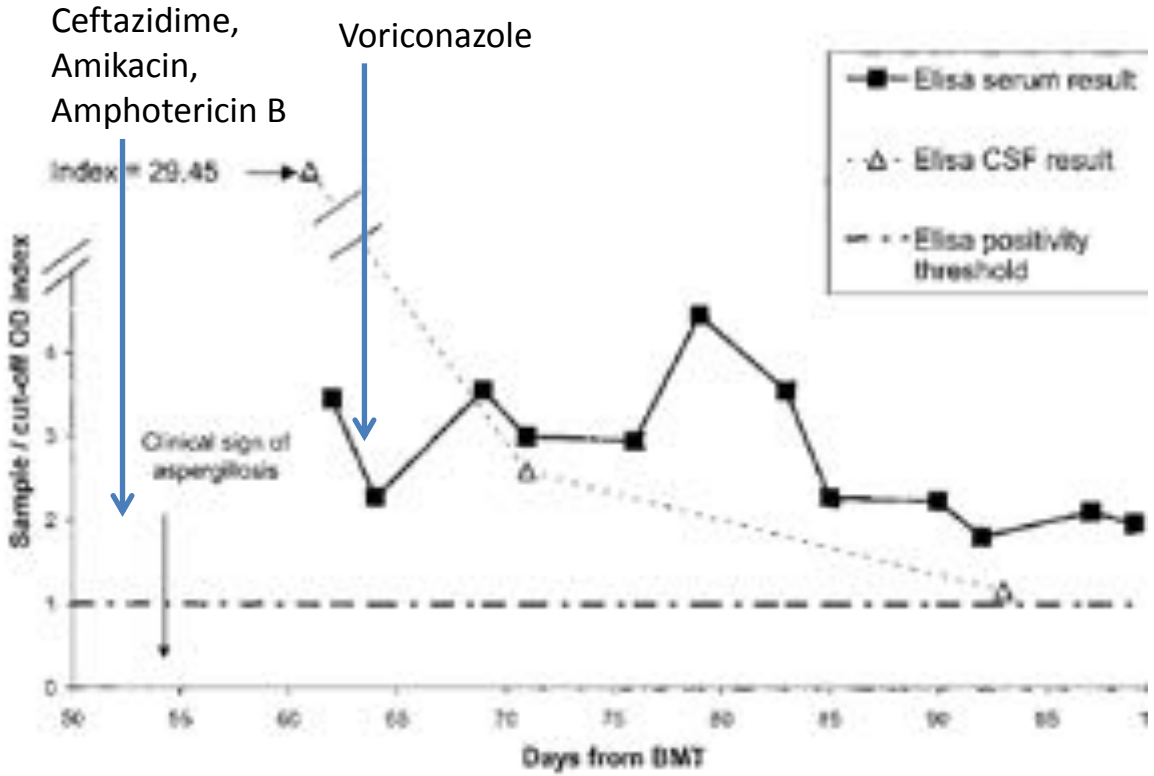


Fig. 4. Galactomannan levels (OD index) in serum and CSF samples.

Machetti M, Zotti M, Veroni L, Mordini N, Van Lint MT, Bacigalupo A, et al. Antigen detection in the diagnosis and management of a patient with probable cerebral aspergillosis treated with voriconazole. Transplant infectious disease : an official journal of the Transplantation Society. 2000;2(3):140-4.

Early diagnosis by CSF GM

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Diagnostic Performance of Galactomannan Antigen Testing in Cerebrospinal Fluid

G. M. Chong,[a] J. A. Maertens,[b] K. Lagrou,[c] G. J. Driessen,[d] J. J. Cornelissen,[e] B. J. A. Rijnders[a]

Erasmus University Medical Center, Department of Internal Medicine, Section of Infectious Diseases, Rotterdam, the Netherlands[a]; KU Leuven, University of Leuven, Department of Microbiology and Immunology, University Hospitals Leuven, Department of Haematology, Leuven, Belgium[b]; KU Leuven, University of Leuven, Department of Microbiology and Immunology, Leuven, Belgium[c]; Erasmus University Medical Center, Sophia Children's Hospital, Subdepartment of Paediatric Infectious Disease and Immunology, Rotterdam, the Netherlands[d]; Erasmus University Medical Center, Department of Haematology, Rotterdam, the Netherlands[e]

Chong GM, Maertens JA, Lagrou K, Driessen GJ, Cornelissen JJ, Rijnders BJ. Diagnostic Performance of Galactomannan Antigen Testing in Cerebrospinal Fluid. Journal of clinical microbiology. 2016;54(2):428-31.

Early diagnosis by CSF GM

	Value (%) with CSF GM ODI Cutoff of					
Parameter	**0.5**	**1.0**	**2.0**	3.0	4.0	5.0
Sensitivity	88.2	88.2	88.2	76.5	70.6	58.8
Specificity	96.3	96.3	96.3	96.3	96.3	96.3
PPV	93.8	93.8	93.8	92.9	92.3	90.9
NPV	92.9	92.9	92.9	86.7	83.9	78.8

- Good diagnostic performance when an Optic Density Index (ODI) cutoff of 0.5 to 2.0 was used
- Using GM in CSF, cerebral aspergillosis can be diagnosed or virtually ruled out without the need for cerebral biopsy

Chong GM, Maertens JA, Lagrou K, Driessen GJ, Cornelissen JJ, Rijnders BJ. Diagnostic Performance of Galactomannan Antigen Testing in Cerebrospinal Fluid. Journal of clinical microbiology. 2016;54(2):428-31.

But does this help improve survival?

Table 2. Galactomannan detection in CSF samples obtained from patients with CNS aspergillosis.

Study	Classification according to EORTC-MSG criteria [45]	No. of patients	Study design	Underlying condition	Galactomannan detection method	No. of patients positive for galactomannan	Outcome
Kami et al., 1999 [65]	Proven	5	NR	Hematologic malignancy	Pastorex and Platelia	4	NR
Verweij et al., 1999 [63]	Probable	1	Case report	Bilateral mastoidectomy	Platelia	1	Cured
Machetti et al., 2000 [66]	Probable	1	Case report	BMT	Platelia	1	Died
Nenoff et al., 2001 [69]	Proven	1	Case report	Diabetes mellitus type II	Pastorex	1	Died
Viscoli et al., 2002 [32]	Probable	5	Prospective	BMT	Platelia	5	Died (all)
Moling et al., 2002 [70]	Probable	1	Case report	Chronic alcohol abuse	Pastorex and Platelia	1	Cured

NOTE. BMT, bone marrow transplantation; EORTC-MSG, European Organization for Research and Treatment of Cancer Mycoses Study Group; NR, not reported; Pastorex, latex agglutination test; Platelia, sandwich ELISA.

Klont RR, Mennink-Kersten MA, Verweij PE. Utility of Aspergillus antigen detection in specimens other than serum specimens. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2004;39(10):1467-74.

Antifungal treatment

TREATMENT OF ASPERGILLOSIS					
Indication	Primary treatment	Evidence Level	Precautions	Secondary Treatment	Comments
Invasive	Voriconazole	AI	Drug interactions (especially with rifampicin), renal failure (IV only)	Amphotericin B, Caspofungin, Posaconazole, Micafungin	As primary therapy Voriconazole carries 20% more responses than Amphotericin B. If azole prophylaxis fails it is unclear whether a class change is required for therapy
Prophylaxis	Itraconazole solution, posaconazole	AI	Diarrhoea and vomiting with Itraconazole, vincristine interaction	Micafungin, aerosolzied Amphotericin B	Some centres monitor plasma levels of Itraconazole
ABPA	Itraconazole	AI	Some glucocorticoid interactions, including with inhaled formulations	Voriconazole	Long-term therapy is helpful in most patients. Others can discontinue treatment. No evidence indicates whether or not progression to bronchiectasis/fibrosis
Single Aspergilloma	Surgery	BII	Multi-cavity disease: poor outcome of surgery; medical therapy preferable	Itraconazole, Voriconazole, intra-cavity Amphotericin B	Single large cavities with an aspergilloma are best resected
Chronic pulmonary	Itraconazole	BII	Poor absorption of capsules with proton pump inhibitors or H2 blockers	Voriconazole, IV Amphotericin B	Resistance may emerge during treatment, especially if plasma drug levels are sub-therapeutic

DL Kasper, AS Fauci. Harrison's Infectious Disease.

Voriconazole VS. amphotericin B

The New England Journal of Medicine

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

RAOUL HERBRECHT, M.D., DAVID W. DENNING, F.R.C.P., THOMAS F. PATTERSON, M.D., JOHN E. BENNETT, M.D., REGINALD E. GREENE, M.D., JÖRG-W. OESTMANN, M.D., WINFRIED V. KERN, M.D., KIEREN A. MARR, M.D., PATRICIA RIBAUD, M.D., OLIVIER LORTHOLARY, M.D., PH.D., RICHARD SYLVESTER, SC.D., ROBERT H. RUBIN, M.D., JOHN R. WINGARD, M.D., PAUL STARK, M.D., CHRISTINE DURAND, M.D., DENIS CAILLOT, M.D., ECKHARD THIEL, M.D., PRANATHARTHI H. CHANDRASEKAR, M.D., MICHAEL R. HODGES, M.D., HARAN T. SCHLAMM, M.D., PETER F. TROKE, PH.D., AND BEN DE PAUW, M.D., FOR THE INVASIVE FUNGAL INFECTIONS GROUP OF THE EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER AND THE GLOBAL ASPERGILLUS STUDY GROUP*

Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. The New England journal of medicine. 2002;347(6):408-15.

Better efficacy with voriconazole than amphotericin B

TABLE 2. SITE OF THE INFECTION, DEGREE OF CERTAINTY, AND EVIDENCE SUPPORTING BASE-LINE DIAGNOSIS IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

VARIABLE	VORICONAZOLE GROUP (N=144)	AMPHOTERICIN B GROUP (N=133)
	no. (%)	
Site of the infection		
Lung only	123 (85.4)	117 (88.0)
Sinus	8 (5.6)	7 (5.3)
Cerebral*	5 (3.5)	5 (3.8)
Disseminated†	4 (2.8)	1 (0.8)
Other	4 (2.8)	3 (2.3)
Level of certainty of the diagnosis of aspergillosis		
Definite‡	67 (46.5)	41 (30.8)
Probable	77 (53.5)	92 (69.2)
Initial evidence of aspergillosis§		
Positive finding on microscopy	56 (38.9)	46 (34.6)
Positive culture	84 (58.3)	65 (48.9)
Positive histologic examination	35 (24.3)	22 (16.5)
Halo or air-crescent sign only	46 (31.9)	49 (36.8)

*Category includes those with other organ involvement.

†Category excludes those with cerebral involvement.

‡There were significantly more definite cases in the voriconazole group ($P=0.01$).

§Some patients had more than one type of biologic evidence.

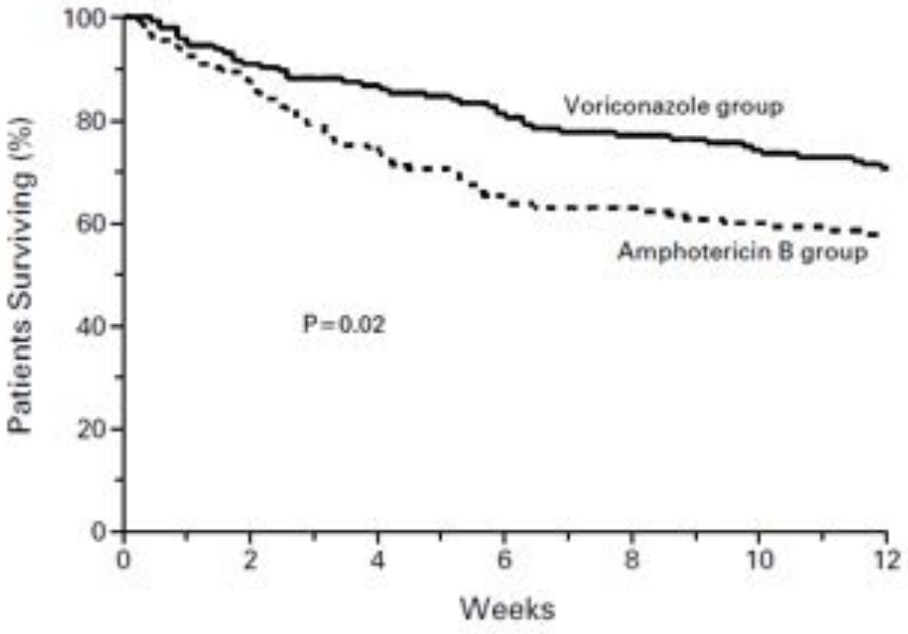
TABLE 3. RESPONSE RATE AT WEEK 12 IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

RESPONSE	VORICONAZOLE GROUP (N=144)	AMPHOTERICIN B GROUP (N=133)
	no. (%)	
Successful outcome*	76 (52.8)	42 (31.6)
Complete response	30 (20.8)	22 (16.5)
Partial response	46 (31.9)	20 (15.0)
Unsuccessful outcome	68 (47.2)	91 (68.4)
Stable disease	8 (5.6)	8 (6.0)
Failure of therapy	55 (38.2)	78 (58.6)
Indeterminate	5 (3.5)	5 (3.8)

*The 95 percent confidence interval around the difference in successful outcomes (stratified according to study) was 10.4 to 32.9 percent.

Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. The New England journal of medicine. 2002;347(6):408-15.

Improved outcome with Voriconazole



No. at Risk							
Voriconazole	144	131	125	117	111	107	102
Amphotericin B	133	117	99	87	84	80	77

Figure 2. Survival Curves for the Modified Intention-to-Treat Population According to Treatment Group.

The P value was calculated by the log-rank test.

Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. The New England journal of medicine. 2002;347(6):408-15.

Voriconazole - Better CNS penetration

- Voriconazole penetrates into the CNS in humans with a cerebrospinal fluid-to-plasma ratio of 0.22 to 1. In addition, high voriconazole brain tissue levels (11.8 ug/g and 58.5 ug/g) were found at autopsy in 2 patients with pulmonary aspergillosis, indicating that voriconazole is enriched in brain tissue.

  Lutsar I. Clinical infectious diseases. 2003;37(5):728-32.

- Caspofungin brain to plasma ratio is 0.2 for maximal concentration at 24 hour and 0.1 for AUC over 24 hours in animal study

  Hajdu R. Antimicrobial agents and chemotherapy. 1997;41(11):2339-44.

- Much lower recoveries of amphotericin B in brain (0.07 – 0.2%), compared with other organs, e.g. lung (8.3 – 44.1%), spleen (0.4 – 7.3%) in cancer patients with suspected or documented fungal infection

  Collette N. The Journal of antimicrobial chemotherapy. 1991;27(4):535-48.

Take home message

- Optic neuritis, although rare, can be of infectious, ischaemic, neoplastic causes, other than MS/NMO/isolation optic neuritis
- Aspergillosis is difficult to diagnose from culture, galactomannan and histology may provide opportunity for earlier diagnosis
- Voriconazole is now the standard treatment