AMSER Rad Path Case of the Month:

29-year-old Male with New Onset Seizure

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Patient Presentation

Clinical history

29 y/o male with pmhx of celiac disease, anal fissures s/p sphincterotomy, anxiety, major depression who had a recent history of subjective increased anxiety and intermittent “panic attacks” later described as blank stares associated with unresponsiveness. He presented to the ED after witnessed collapse and “whole body shakes” followed by confusion and grogginess. No evidence of tongue biting or incontinence at that time. Computed tomography of the head (CTH) raised concern for intracranial mass.

Pertinent social history

No significant social history

Pertinent Labs and Work Up

Patient’s blood work was within normal limits

An EEG was negative for any epileptiform discharges

Pertinent physical exam findings

Complete neurologic exam was intact

What Images Should Be Ordered?

ACR Appropriateness Criteria

American College of Radiology
ACR Appropriateness Criteria®
Seizures and Epilepsy[2]

Variant 1: **New-onset seizure. Unrelated to trauma. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
CT head without IV contrast	Usually Appropriate	☢☢☢
MRI head without IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	May Be Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
MEG	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
HMPAO SPECT or SPECT/CT brain ictal and interictal	Usually Not Appropriate	☢☢☢

CTH ordered by OSH ED prior to transfer

MRI head w and w/o contrast ordered by Neurosurgery

*CTH is almost always appropriate. MRI head w and w/o was ordered due to CTH suspicion for underlying mass.
**CTA and fMRI Brain were ordered as part of preoperative work up once mass was discovered

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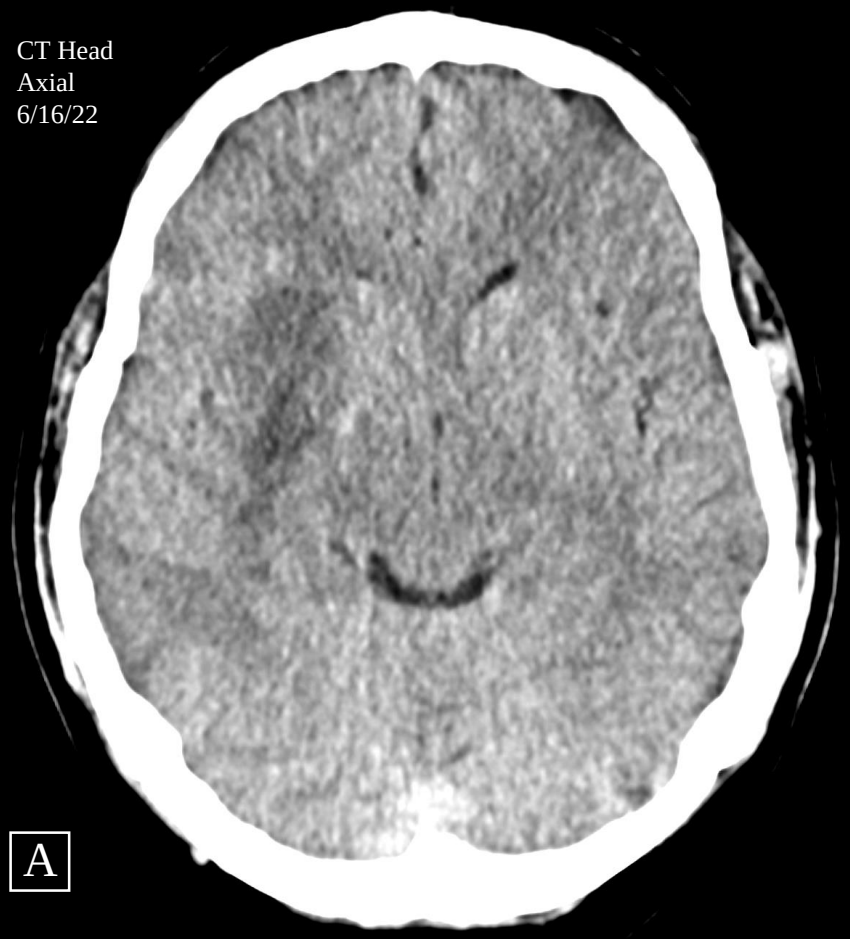
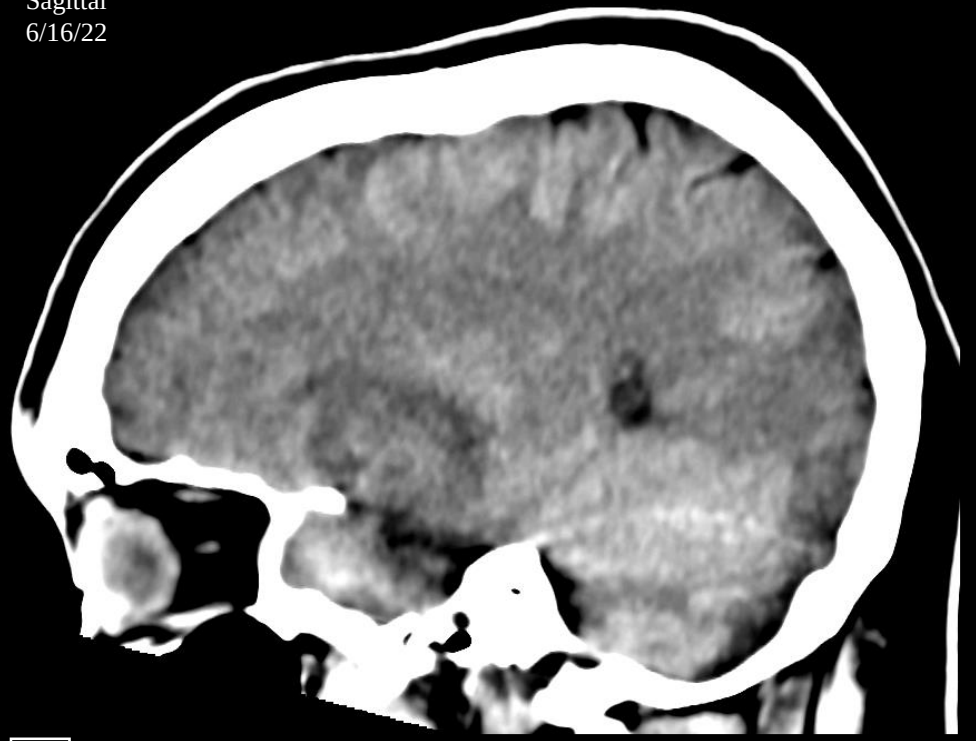
Radiology Images (not labeled)

CT Head
Axial
6/16/22



A

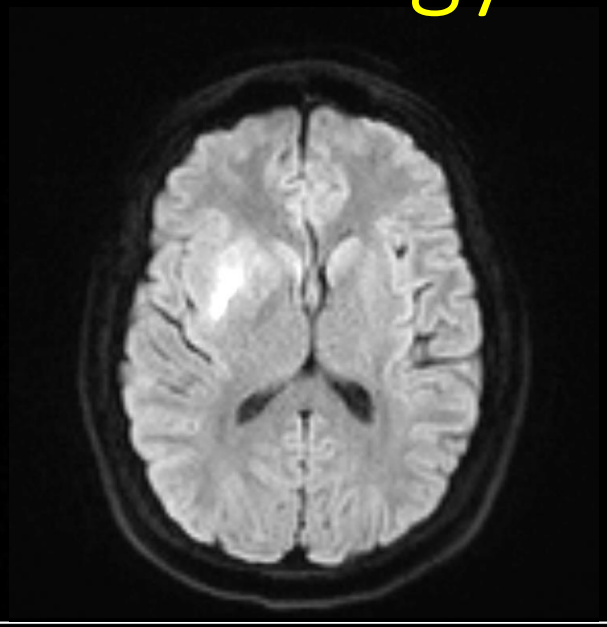
CT Head
Sagittal
6/16/22



B

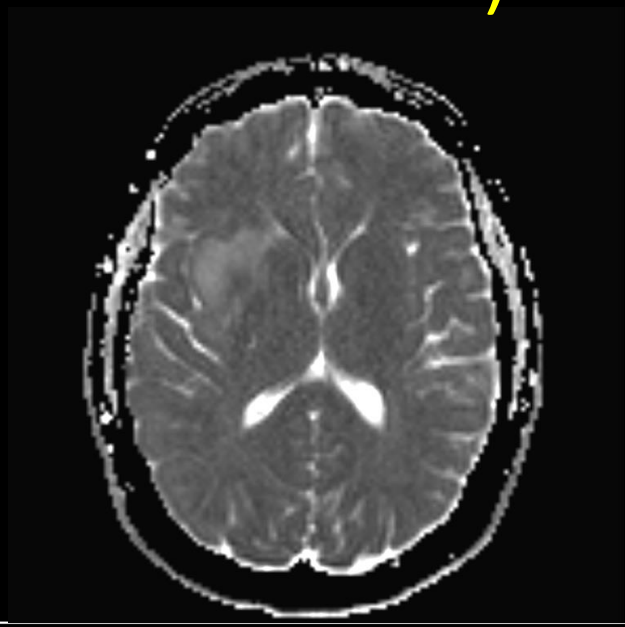
Radiology Images (not labeled)

MRI Brain DWI
Axial
6/17/22



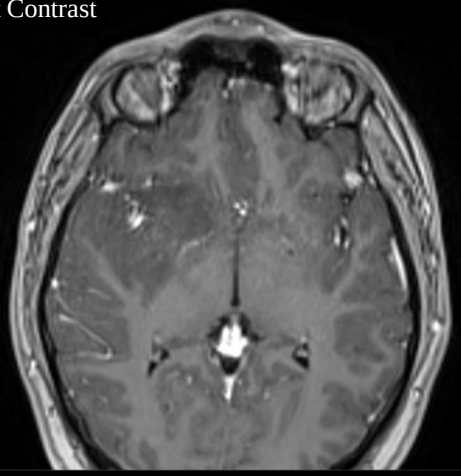
A

MRI Brain ADC
Axial
6/17/22



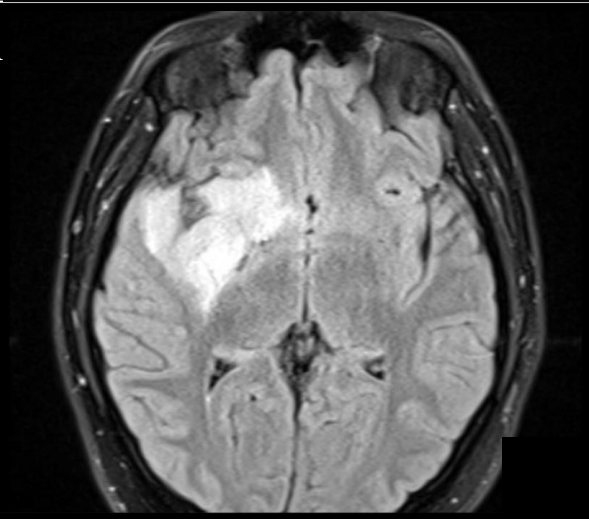
B

MRI Brain T1 Post Contrast
Axial
6/17/22



C

MRI Brain FLAIR
Axial
6/17/22



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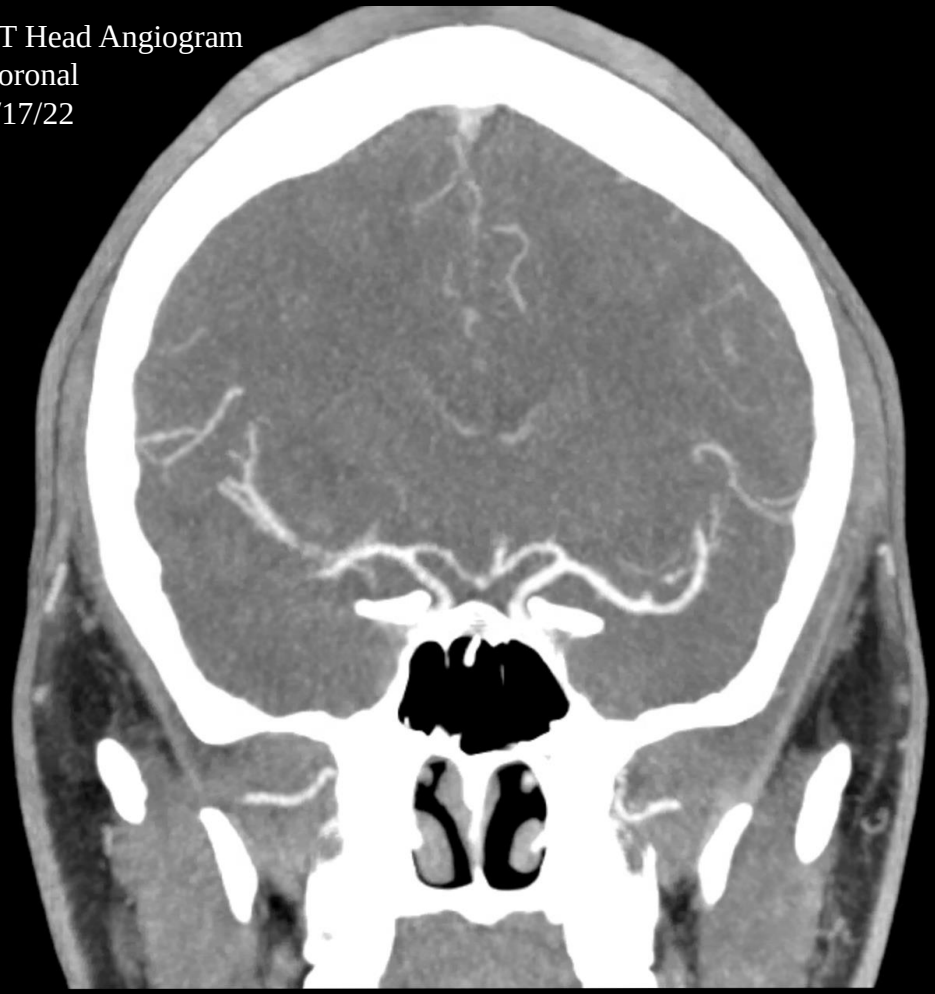
Radiology Images (not labeled)

CT Head Angiogram
Coronal
6/17/22



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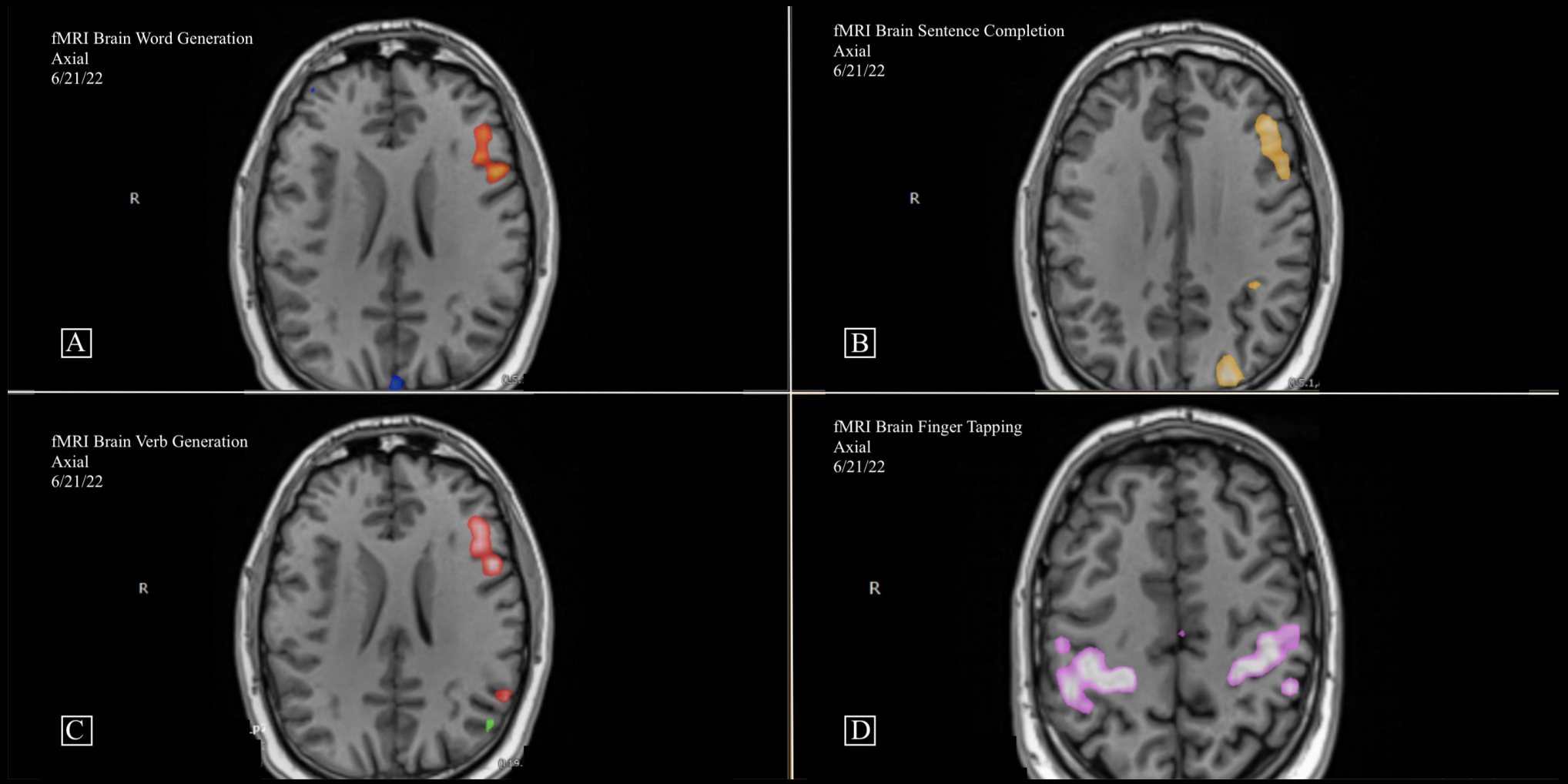
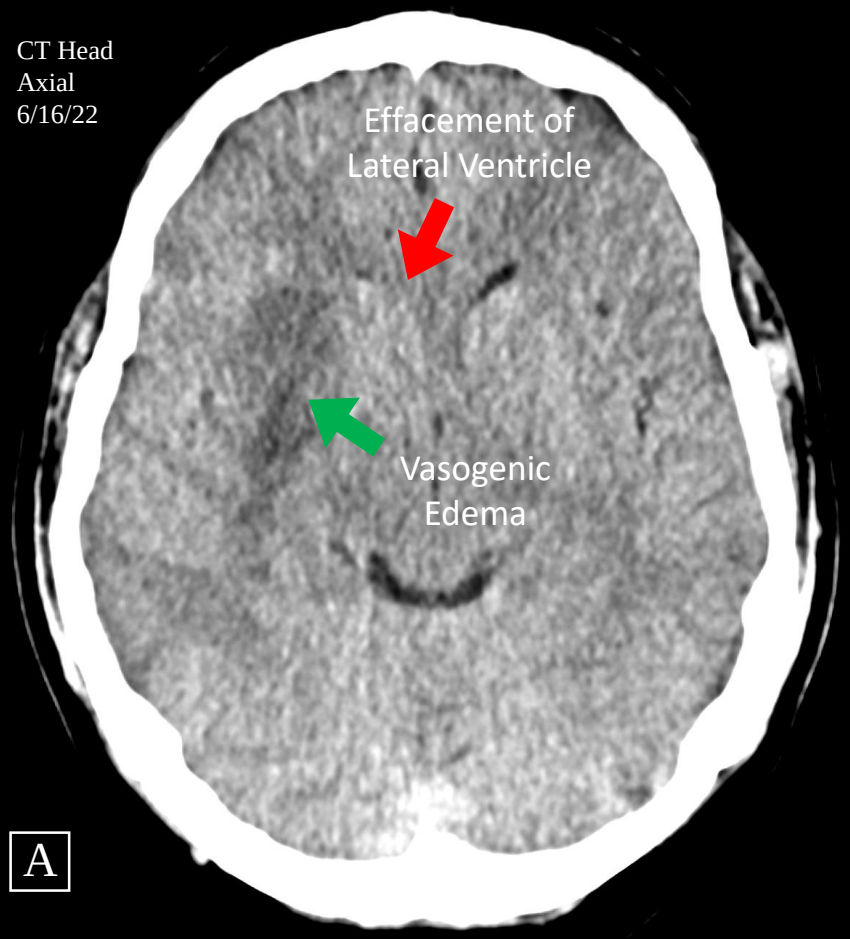


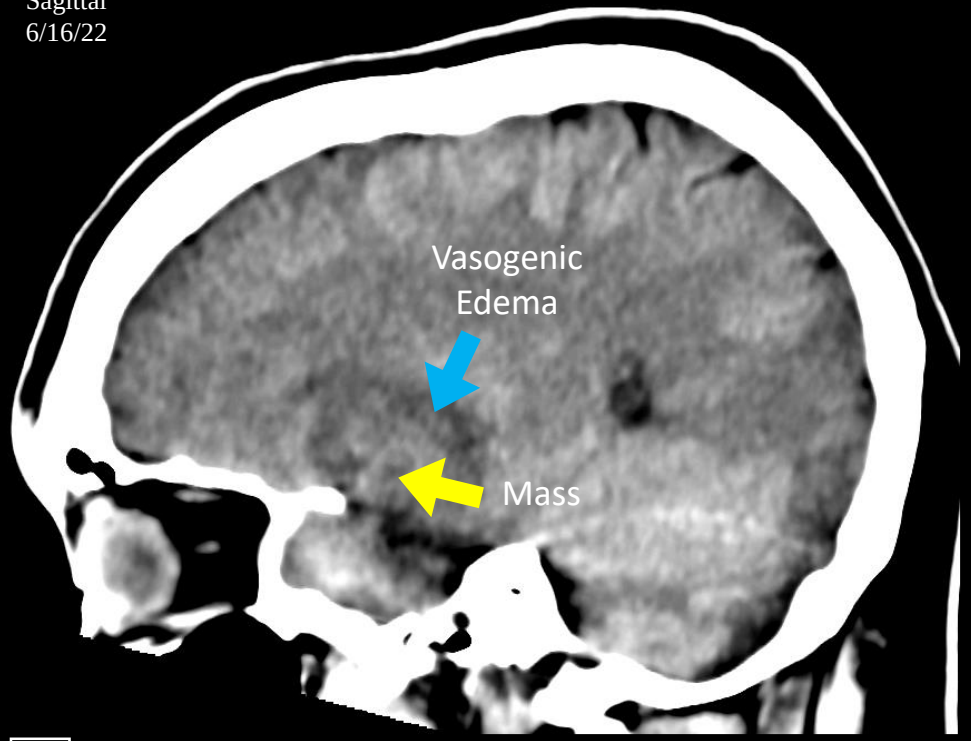
Radiology Images (labeled)

CT Head
Axial
6/16/22



A

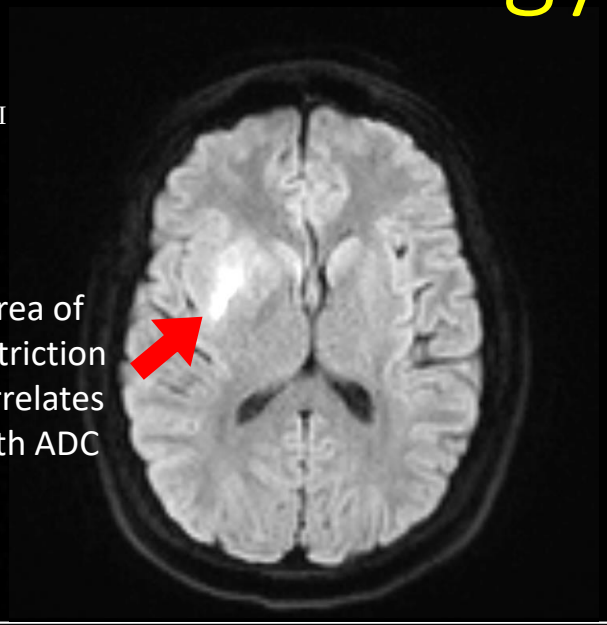
CT Head
Sagittal
6/16/22



B

Radiology Images (labeled)

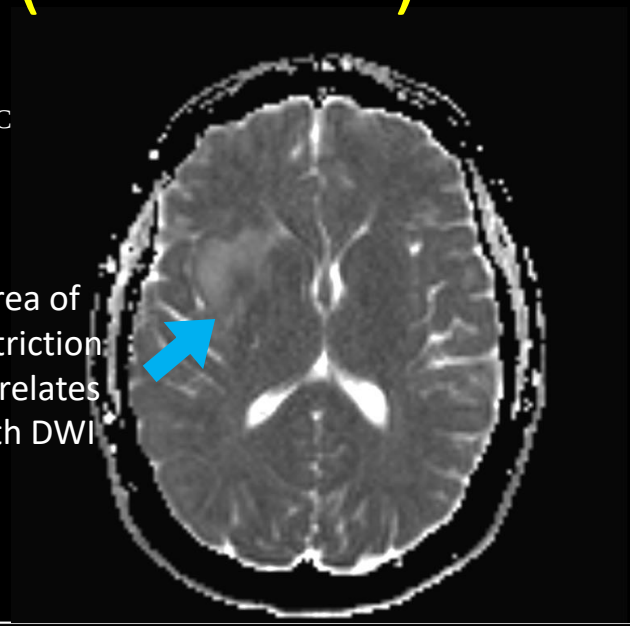
MRI Brain DWI
Axial
6/17/22



Area of restriction correlates with ADC

A

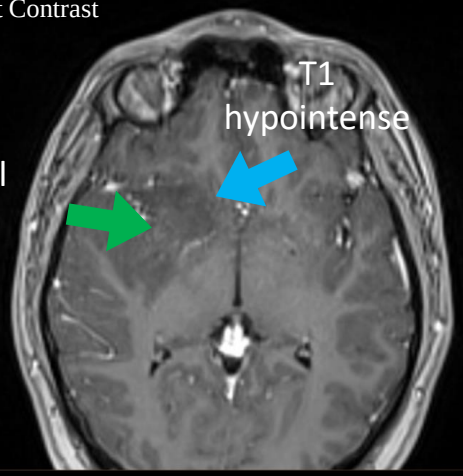
MRI Brain ADC
Axial
6/17/22



Area of restriction correlates with DWI

B

MRI Brain T1 Post Contrast
Axial
6/17/22

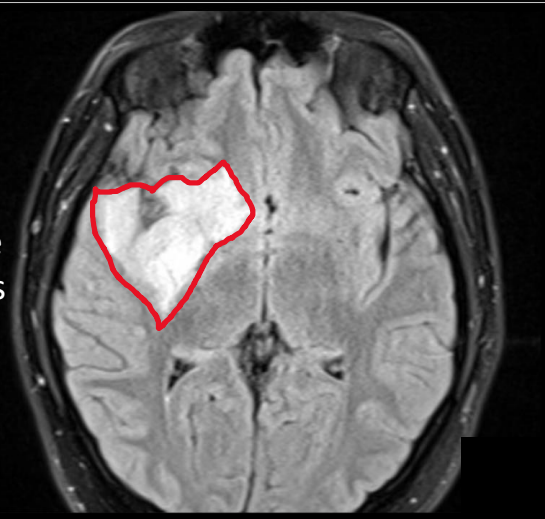


T1 hypointense

Mild patchy central enhancement

C

MRI Brain FLAIR
Axial
6/17/22



T2/FLAIR hyperintense 5.38 cm mass

D

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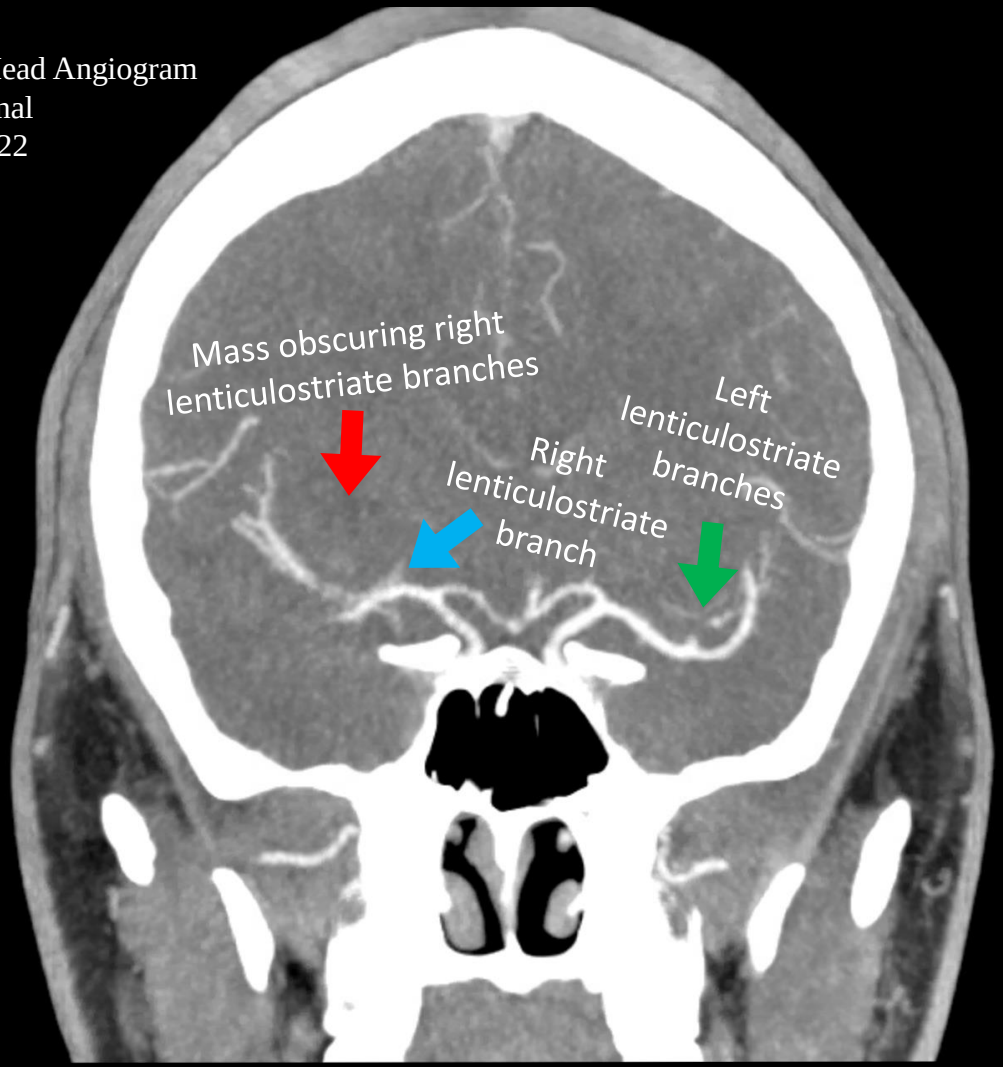
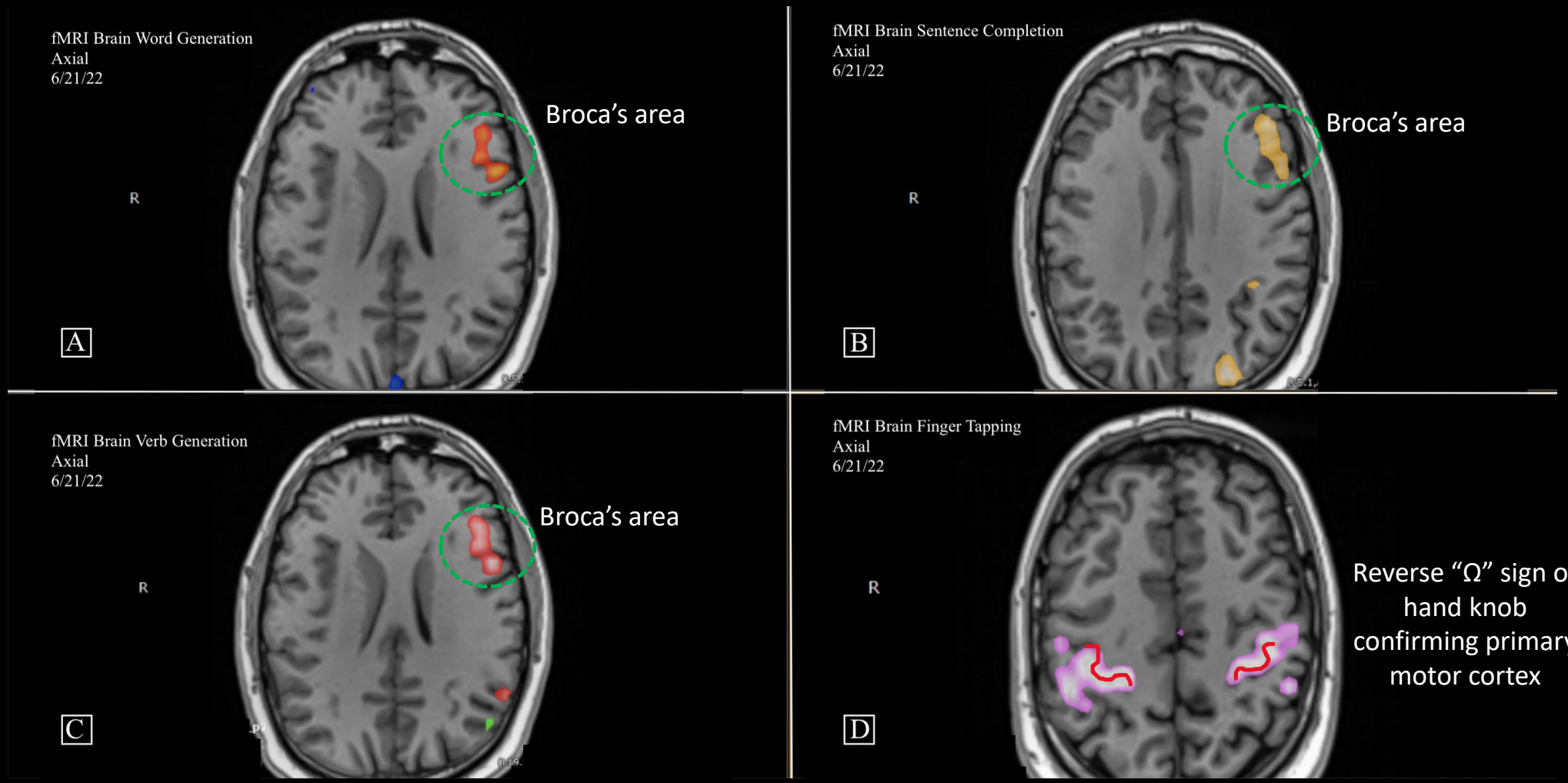
Radiology Images (labeled)

CT Head Angiogram
Coronal
6/17/22



Radiology Images (labeled)



Radiology Summary

OSH CTH: Preliminary scan obtained at OSH ED showed effacement of the right lateral ventricle and a hypodensity in the left insula likely to be vasogenic edema as well as a focus of heterogenous density concerning for an underlying mass.

MRI brain w and w/o contrast: 5.38 x 5.32 x 4.0 cm intra-axial lesion in right frontotemporal region traversing sylvian fissure, T1 hypointense with patchy enhancement, T2/FLAIR hyperintensity, close approximation to right basal ganglia and hypothalamus. Mild focus of restriction seen on DWI correlates with ADC.

Pre-Op CTA: Mass abutting the right distal M1/proximal M2 MCA segments but confirmed patency. Lenticulostriate branches are visible on the left but are obscured by mass on the right concerning for encasement.

fMRI brain: Left-sided language centers confirmed by increased activity during sentence completion, word generation, and verb generation in the left Broca's area with no activity on the right side. Increased activity with finger tapping over the bilateral primary motor cortex confirms hand knob identified by the reverse "Ω" sign without proximity to the mass.

DDX (based on imaging)

1. Metastatic disease

Most common cause of intracranial masses. Usually well circumscribed, rim enhancing, and associated with vasogenic edema.

2. Glioma

Most common primary intra-axial mass. Low grade: Infiltrative, T2/FLAIR hyperintense, typically does not enhance, rarely associated with edema. High Grade: Infiltrative, rim enhancing, centrally necrotic, associated with vasogenic edema.

3. Lymphoma

Typically, rare in CNS especially compared to glioma. T2 hypointense/Isointense, enhances homogenously, significant diffusion restriction.

4. Acute Disseminated Encephalomyelitis (ADEM)

Autoimmune inflammatory condition commonly resulting in diffuse demyelination following nonspecific infection.

5. Progressive Multifocal Leukoencephalopathy (PML)

Viral infection caused by JC virus that is almost exclusively seen in immunocompromised hosts.

6. Multiple Sclerosis (MS)

Autoimmune demyelination that must be disseminated in time and space.

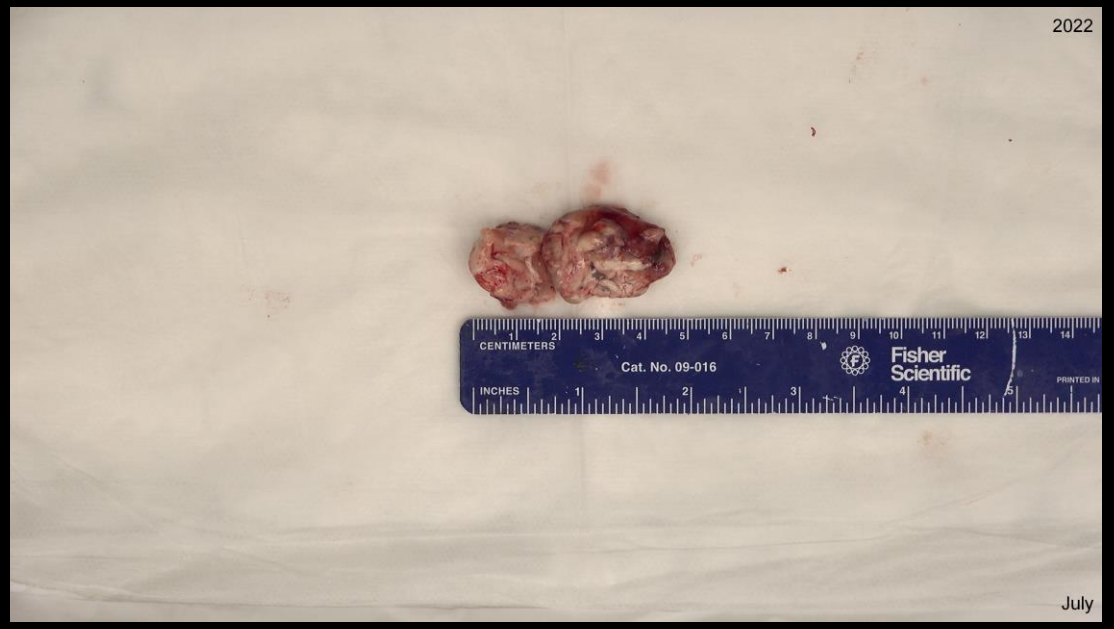
7. Tuberous Sclerosis

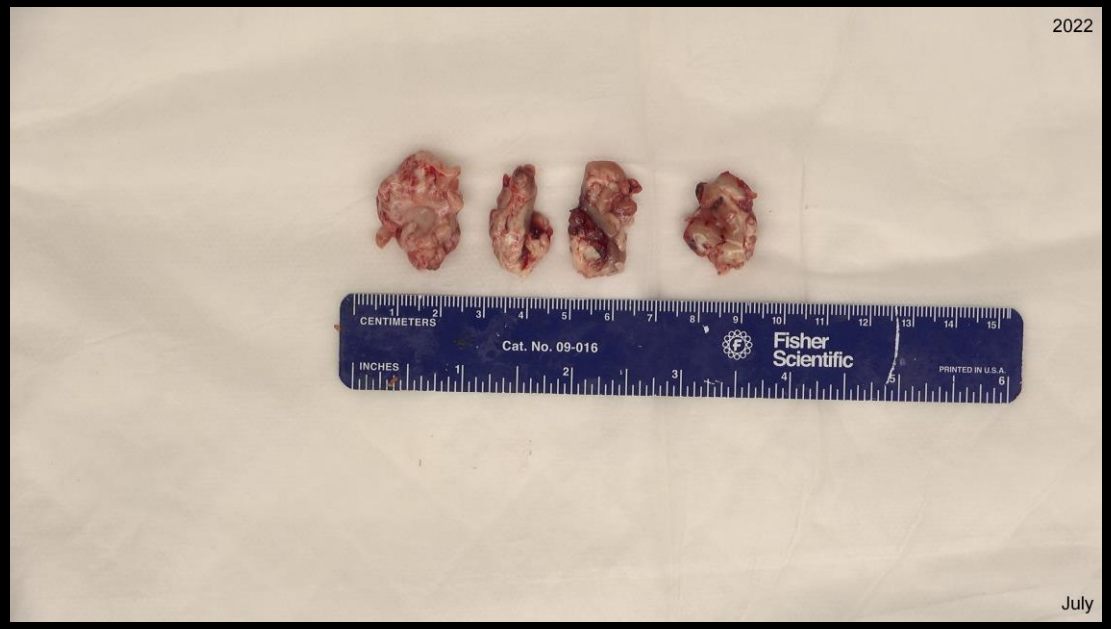
Genetic disorder associated with multisystem tumor proliferation.

8. Hemorrhage/Infarct

Commonly can be mistaken for true masses due variability in appearance, enhancement, and associated mass effect depending on location, size, and timing.[7]

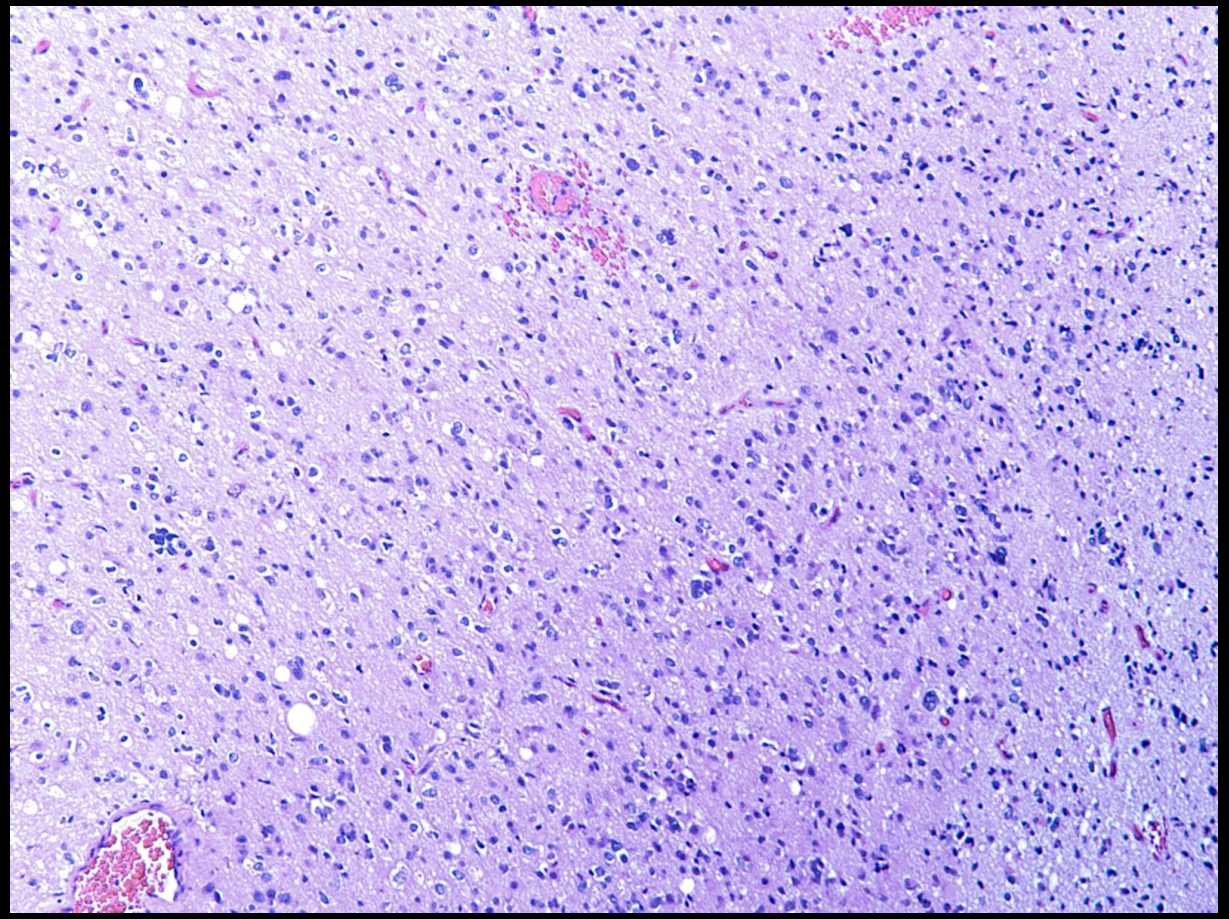
Gross Specimen



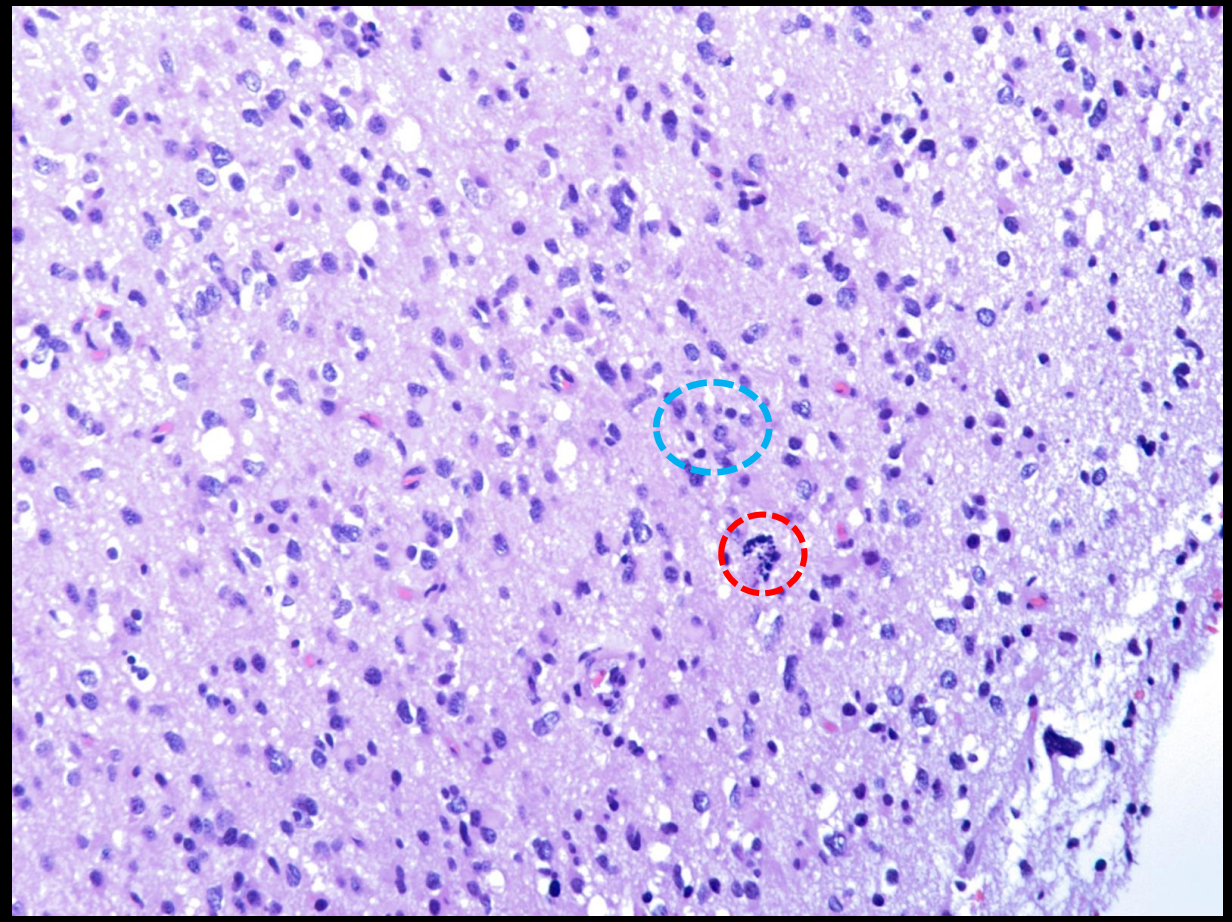


Small pieces of glioma. Tumor is grey-tan color, but relatively difficult to distinguish from normal brain tissue. Use of cautery accounts for darkening of tissue.

Histology



(10x) H&E. Hypercellular with uneven distribution of cellularity indicative of glial neoplasm. No evidence of necrosis or vascular proliferation.



(20x) H&E. Uneven distribution of hypercellularity with dense fibrillar background. Perineuronal satellitosis (blue circle) indicative of infiltrative diffuse glioma. Nuclear atypia, scattered mitotic figures and clear abnormal mitoses (red circle) indicative of high-grade glioma.

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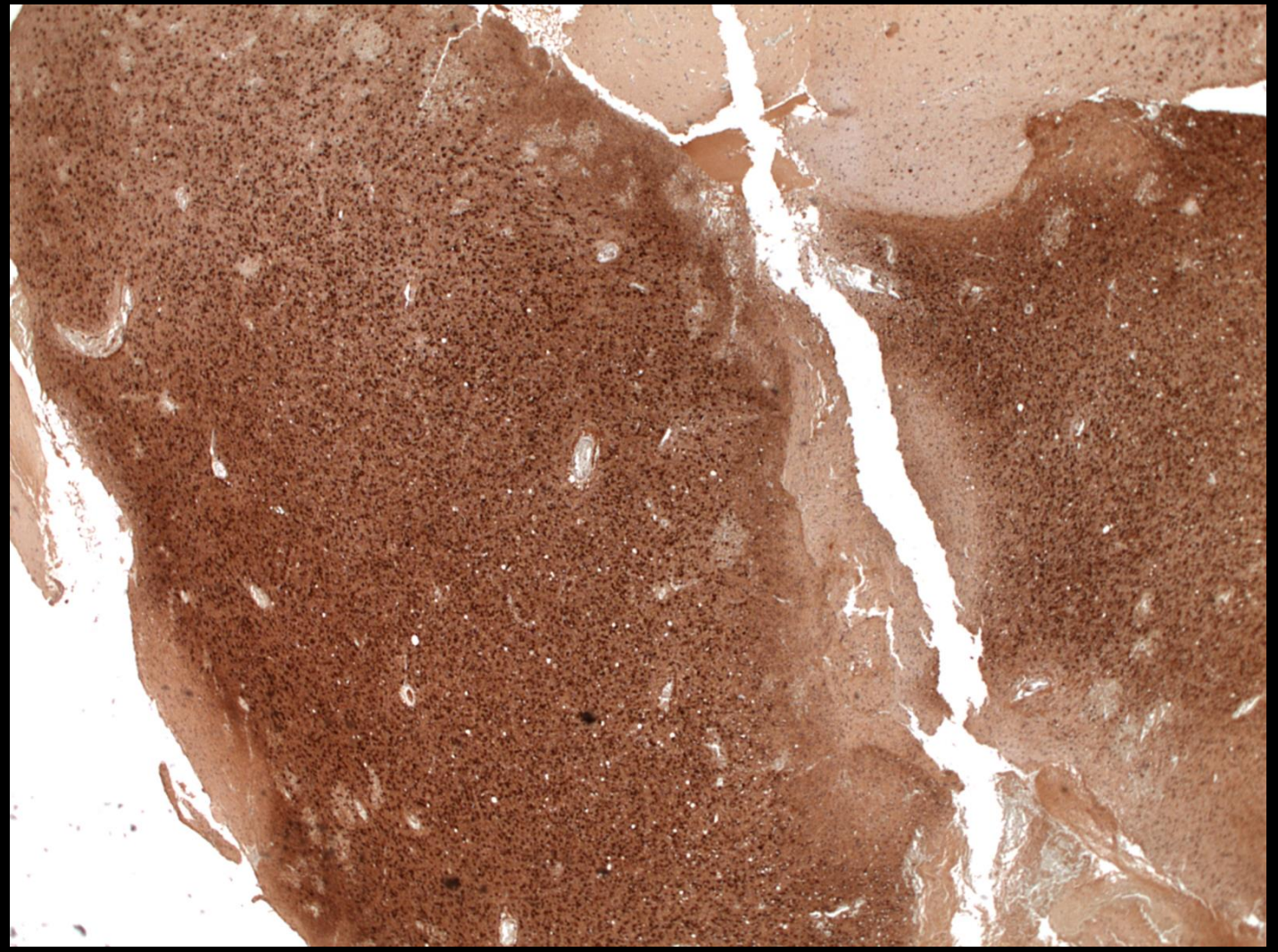
Immunohistochemistry



Positive stain for IDH Mutant

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Pathology Summary

Permanent section: revealed features consistent with high grade glial neoplasm[8] including

Glial Nature:
1. Hypercellular with uneven distribution of cellularity.
2. Dense fibrillar background
3. Perineuronal satellitosis indicating diffuse infiltrative process

Grading:
1. Presence of nuclear atypia
2. Diffusely scattered mitotic figures and abnormal mitoses
3. Lack of necrosis or vascular proliferation

Immunohistochemistry: IDH mutant (pictured), ATRX expression loss and p53 mutant expression (most common genetic mutations in grade 3 astrocytomas[6]).

Classification: Glial microscopic morphology in combination with loss of ATRX and presence of P53 staining indicates an astrocytic neoplasm with high grade features. Despite lack of necrosis and vascular proliferation, molecular testing for CDKN2A/2B loss is required to rule out grade 4.[10]
IDH mutant type and methylation were present.

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Final Dx:

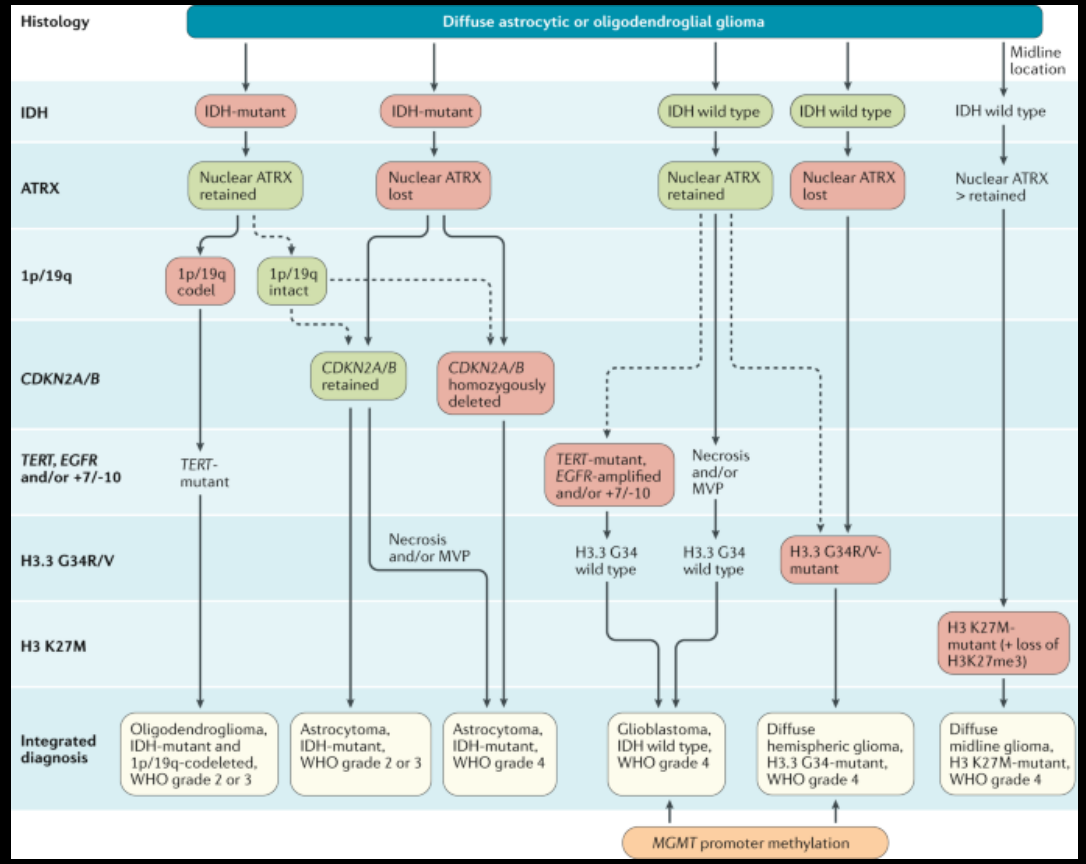
Astrocytoma, IDH mutant CNS WHO grade 3
(previously Anaplastic Astrocytoma, IDH mutant WHO grade III)

Case Discussion

In 2021, the WHO changed how they classify brain tumors. They are now classified and graded by various combinations of histologic and genetic markers.

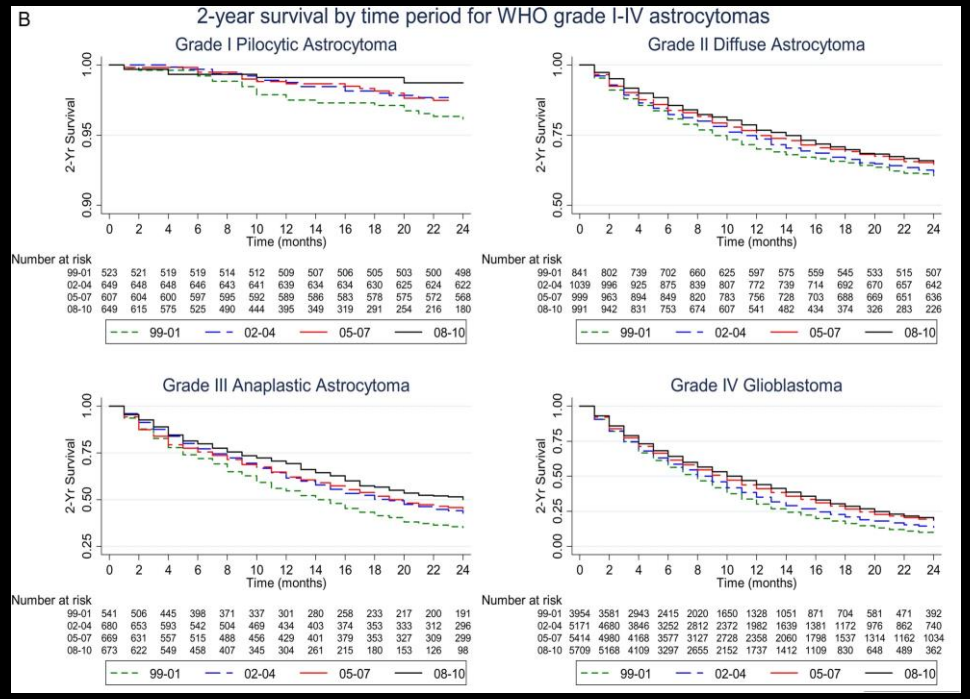
Ex. Diffuse astrocytomas with CDKN2A/2B codeletion without histologic necrosis or vascular proliferation is now grade 4.[10]

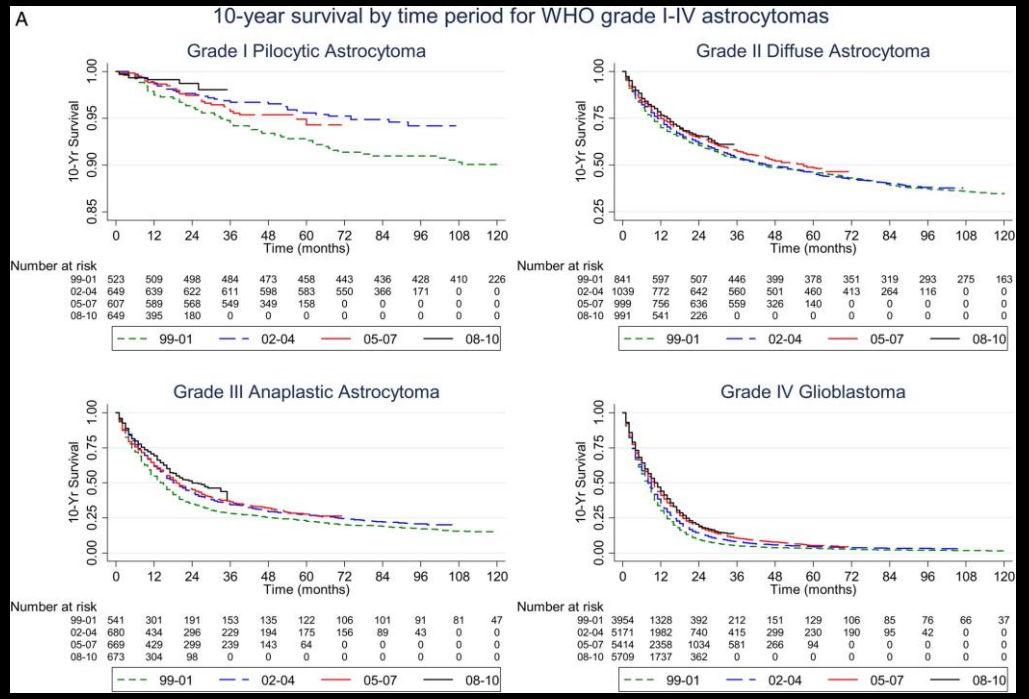
Algorithm showing new 2021 WHO classification for gliomas based on genetic markers[11]



Case Discussion

Grade 2, 3, and 4 gliomas are not curable regardless of gross total resection, but lower grade at the time of diagnosis is associated with longer survival.





Kaplan Meier curves for 2-year and 10-year survival based on previous WHO grades. All cause mortality at 2 years was 5.86%, 51.18%, 67.4%, and 85.85% for grades I-IV, respectively.[1]

Case Discussion

Current treatment guidelines recommend maximal safe resection followed by adjuvant radiation and then adjuvant chemotherapy with temozolomide for 12 cycles is standard of care.[11]

IDH mutant type and the presence of methylation are good prognostic factors due to increased sensitivity to radiation and chemotherapy.[7]

Pertinent to our patient, the CATNON trial showed adjuvant radiotherapy followed by 12 weeks of temozolomide increased survival in IDH mutant grade 3 astrocytoma, but not in IDH wild-type. Concurrent temozolomide with radiation only marginally increases survival.[11]

All gliomas progress over time with 74% of grade 2 astrocytomas transforming into grade 3 or 4 at recurrence. Time to recurrence is prolonged in patients initially diagnosed with grade 2 and 3 lesions.[5]

Secondary grade 4 lesions and non grade 4 lesions recurred at 2.9 and 4.0 years, respectively, compared to 1.1 years for de novo grade 4. Progression to grade 4 has similar overall survival to de novo grade 4 lesions from time of recurrence, about 7-8 months.[5]

Case Discussion

Future Directions

Gliomas have been shown to shed extracellular vesicles into the CSF potentiating a biomarker to monitor treatment response over time.[3]

Future therapy looks to target Ferroptosis, the process of iron binding induced programmed cell death, regulator genes. Mutations inhibiting this process have been shown to predict glioma progression.[7]

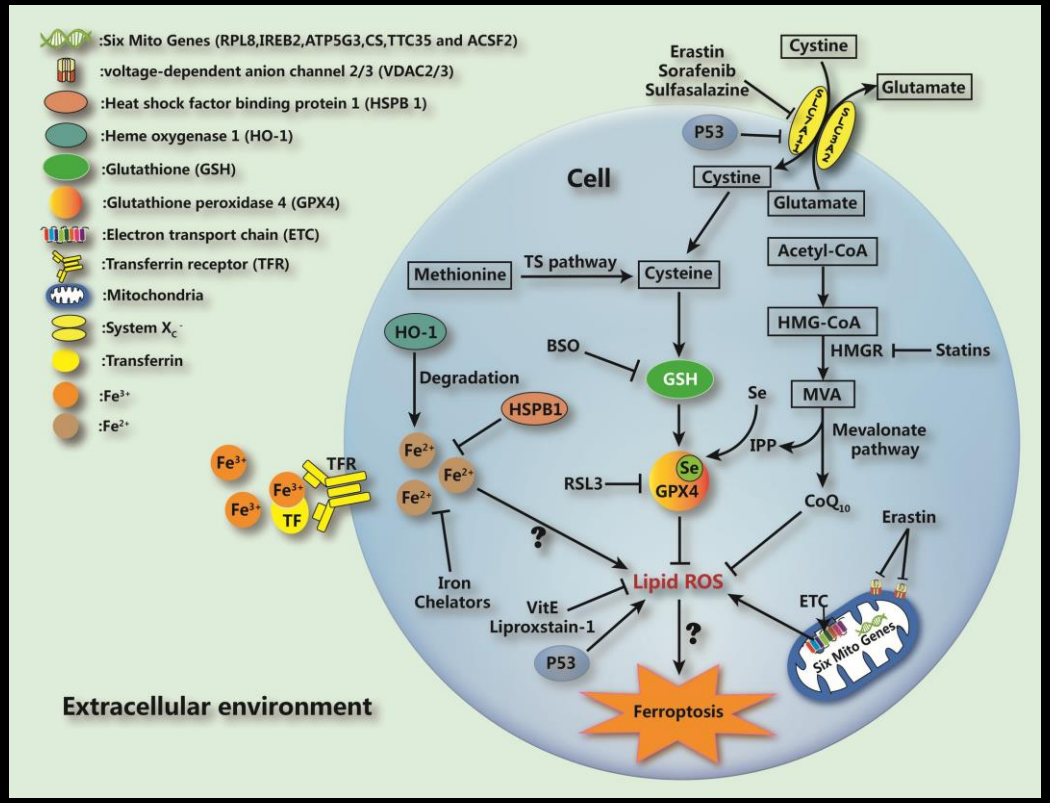


Diagram showing cascades involved in ferroptosis[12]

References:

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