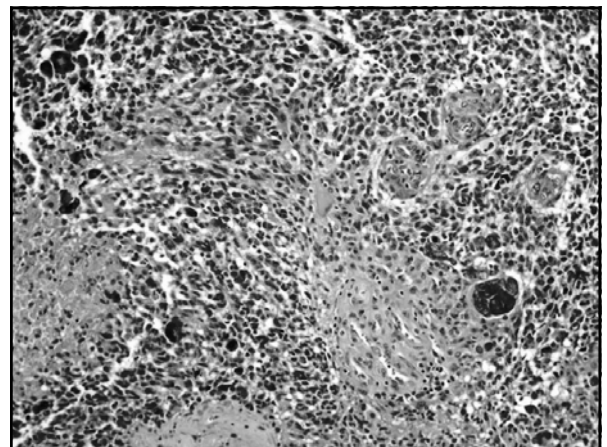
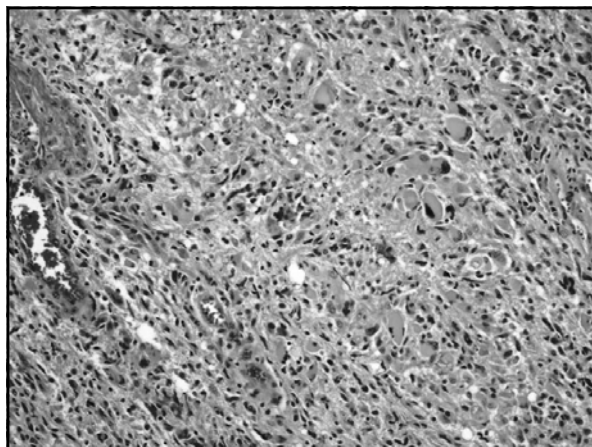
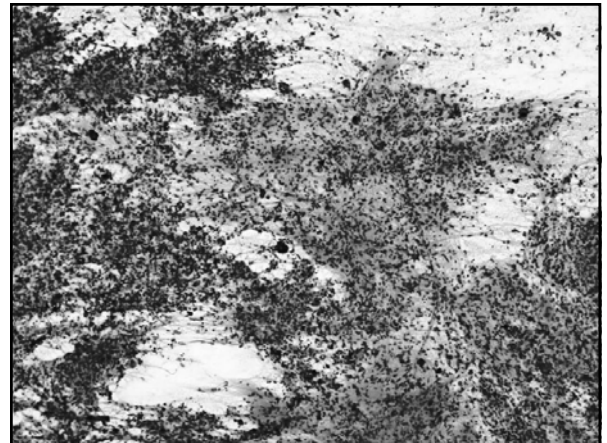
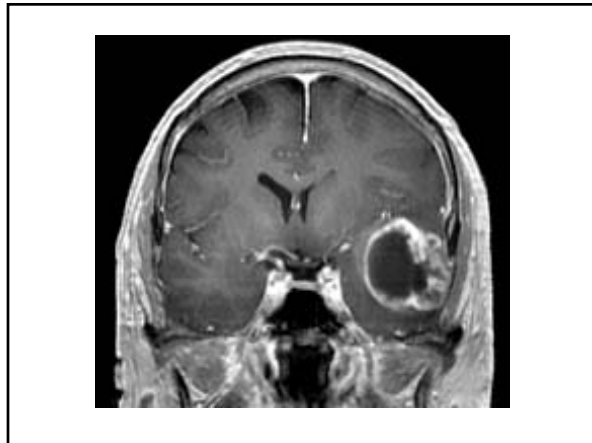


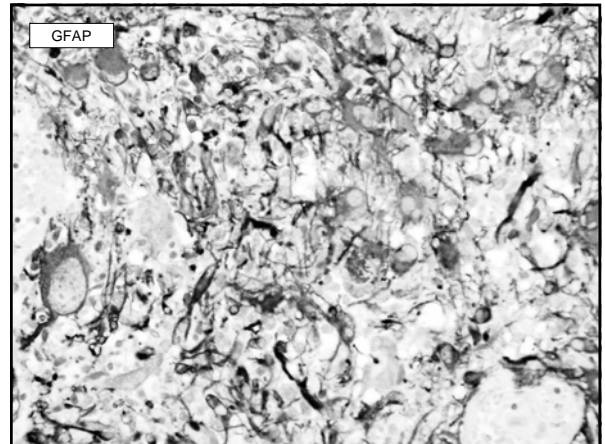
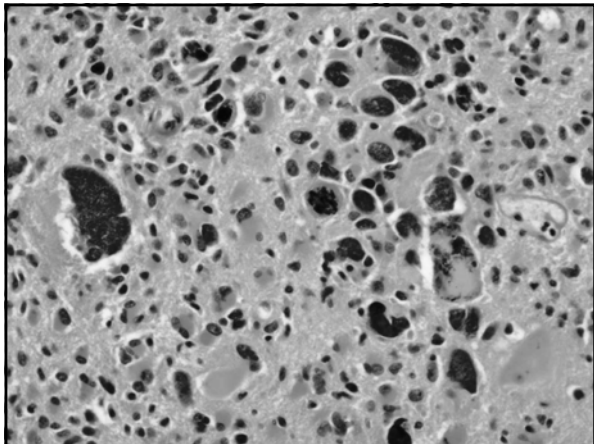
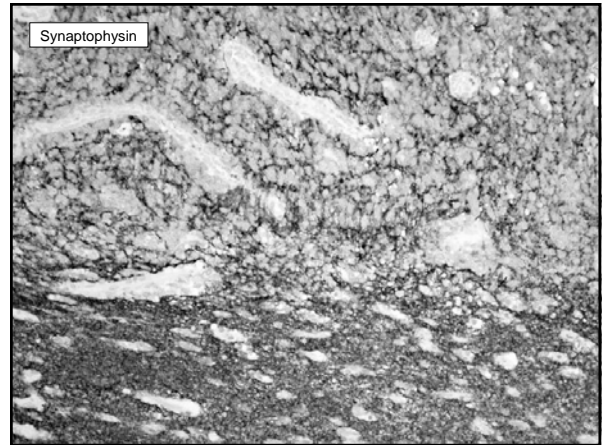
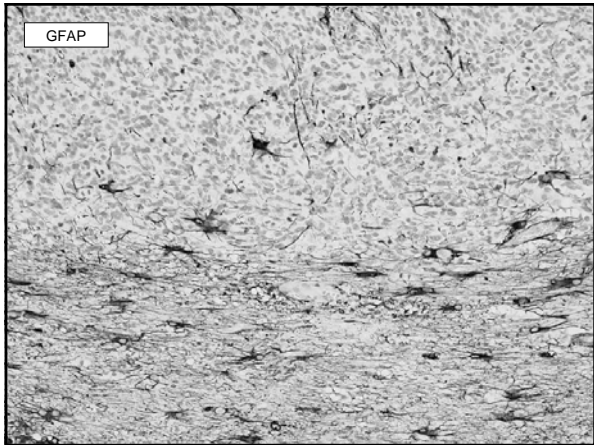
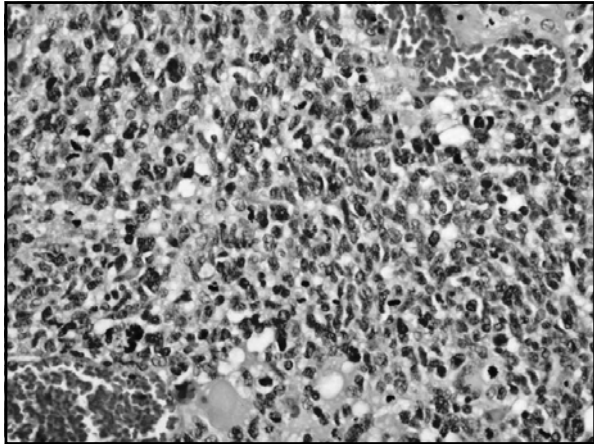
Case #3

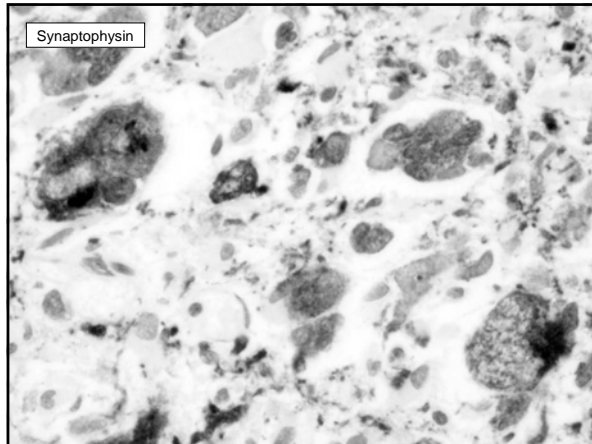
USCAP Neuropathology Evening
Seminar/Companion Meeting

Clinical History

A 71-year-old man presented with a 4-week history of word finding difficulty. An initial screening head CT followed by an MRI scan revealed a large ring-enhancing mass of the left temporal lobe that abutted the dura. The patient was referred to a tertiary care hospital where craniotomy and surgical resection of the mass were performed.







Diagnosis?

- Malignant glioneuronal tumor

Histologic Features

- Features of a high grade malignant neoplasm with nuclear pleomorphism, mitotic activity, vascular proliferation and necrosis
- Both glial and neuronal differentiation as characterized by GFAP and synaptophysin immunoreactivity

Glioneuronal Tumors

- “New entities”
 - Rosette-forming glioneuronal tumor
 - Glioneuronal tumor with neuropil-like islands
 - Papillary glioneuronal tumor
- “Traditional”
 - Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos)
 - Desmoplastic infantile astrocytoma and ganglioglioma
 - Dysembryoplastic neuroepithelial tumor (DNET)
 - Gangliocytoma/ganglioglioma
 - Central neurocytoma and extraventricular neurocytoma
 - Cerebellar liponeurocytoma

“Malignancy” in neuronal/gangliocytic tumors

- Most often seen in tumors with both glial and neuronal/gangliocytic differentiation
- “Malignant” cells are often felt to be of glial origin
- However, mixed glioneuronal phenotypic expression in this category is increasingly recognized and under intense investigation.

Differential Diagnosis and Pitfalls

- The clinical differential diagnosis of a solitary contrast-enhancing mass in an older adult patient is broad, but the most common etiologies are metastatic carcinoma, glioblastoma, and primary central nervous system large B-cell lymphoma; other entities to keep in mind are demyelinating pseudotumor and cerebral abscess.
- The misdiagnosis of demyelinating pseudotumor as diffuse glioma is one of the most common serious diagnostic errors in surgical neuropathology, which can lead to the inappropriate administration of CNS irradiation and/or chemotherapeutic intervention, both of which can have deleterious side effects.

Varlet et al - New Variants of Malignant Glioneuronal Tumors: A study of 40 cases

- All tumors coexpressed glial fibrillary acidic protein and NFP
- Other neuronal markers tested were inconsistently expressed
- No recurrence was observed at the primary site in 36.4% of patients who underwent gross total resection
- Twelve patients (33.3%) developed intra-axial and/or systemic metastases, and 4 were free of disease at 39 to 184 months.
- Gross total surgical resection ($P = 0.001$) and a long duration of symptoms (symptoms > 1 yr; $P = 0.013$) proved to be independent and statistically significant prognostic factors in the multivariate analysis.
- CONCLUSIONS: NFP immunostaining is required to identify MGNTs accurately
- Their distinction from malignant gliomas is of paramount clinical importance, particularly for neurosurgeons, because gross total surgical resection may be curative in some cases.
- MGNTs may account for the long-term survival and/or occurrence of metastases demonstrated in a subset of malignant gliomas.

Vajtai et al - Malignant glioneuronal tumor of the adult cerebrum with neuropil-like islands involving "proliferating nodules": confirmatory report of unusual variant

- Left frontal lobe mass in 59 year old woman
- 70% was conventional GBM
- Several discrete aggregates of non-descript round cells with a primitive appearance were present with smudged contours
- Within individual clusters there were delicate processes but the round cells stained strongly for synaptophysin and were surrounded by GFAP positive astrocytes
- MIB-1 staining positive 9-11% in astrocytic component, the round cell nodules stained positively in approximately 40%

Rodriguez et al - Unusual malignant glioneuronal tumors of the cerebrum of adults: a clinicopathologic study of three cases

- 2 men and 1 woman, ages ranging from 35 – 83
- Epithelioid cells in 3, spindle cells in 1 and undifferentiated small cells in 1
- Necrosis, non-palisading was present in all 3 with brisk mitotic activity
- All immunoreactive for GFAP, S-100, synaptophysin, chromogranin and 2 were positive for Neu-N and neurofilament proteins
- EM showed convincing neurosecretory granules in one case, and some in filament containing cells were immunogold labeled for GFAP

Shibahara et al – Secondary glioblastoma with advanced neuronal phenotype

- 35 year old man with a partially resected astrocytoma (immunoreactive for GFAP with a MIB-1 labeling index of approximately 2%) and treated with post-op radiation and chemotherapy
- Residual/regrowth resected 5 months and then again 8 months later with death at 11 months with subarachnoid and intraventricular dissemination
- Recurrences showed a small blue cell tumor with occasional large multinucleated giant cells
- Recurrences showed high MIB-1 labeling index (80%) and extensive positivity for both synaptophysin and NeuN but NOT for GFAP
- Although initially diagnosed as GBM, may be better classified as a malignant glioneuronal tumor

Summary

- A wide range of diverse morphologies can be seen in high-grade diffuse glioma, and mixed glioneuronal phenotypic expression in this category is increasingly recognized and under investigation.
- The evaluation of CNS neoplasms increasingly relies on the interpretation and integration of panels comprised of several phenotypic markers rather than on single antibodies.
- Oncologic neuropathology remains a dynamic, evolving field in which novel tumor types and subtypes of clinical importance continue to be recognized and characterized.

References

1. Biernat W, Zakrzewski K, Pois L, Liberski PP. Glioneuronal-mesenchymal tumour with malignant transformation. *Poln Neuropathol*. 2007;745(3):140-3.
2. Barbashina V, Salazar P, Ladanyi M, Rosenblum MK, Edgar MA. Glioneuronal tumor with neuropil-like islands (GTNI): a report of 8 cases with chromosome 1p/19q deletion analysis. *Am J Surg Pathol* August 2007 31(8): 1196-2002
3. Vajtai I, Reinert MM. Malignant glioneuronal tumor of the adult cerebrum with neuropil-like islands involving "proliferating nodules": confirmatory report of an unusual variant. *Acta Neuropathologica (Berlin)* 2007 June 113 (6):711-13 Epub April 11 2007
4. Edgar MA, Rosenblum MK. Mixed glioneuronal tumors. Recently described entities. *Arch Pathol Lab Med* 2007 131:228-233.
5. Rodriguez FJ, Scheithauer BW, Robbins PD, Burger PC, Hessler RB, Perry A, Abell-Aleff PC, Mierau GW. Ependymomas with neuronal differentiation: morphologic and immunohistochemical spectrum. *Acta Neuropathol* 2007. 113:313-324.
6. Rodriguez FJ, Scheithauer BW, Port JD. Unusual malignant glioneuronal tumors of the cerebrum of adults: a clinicopathologic study of three cases. *Acta Neuropathol*. 2006 Dec;112(6):727-37. Epub 2006 Sep 7
7. Shibahara J, Fukuyama M. Secondary glioblastoma with advanced neuronal immunophenotype. *Virchows Arch* 2005. 447:665-668.
8. Varlet P, Soni D, Miquel C, Roux FX, Meder JF, Chneiweiss H, Daumas-Duport C. New variants of malignant glioneuronal tumors: a clinicopathological study of 40 cases. *Neurosurgery* 2004 Dec;55(6):1377-91
9. Cenacchi G, Giangaspero F. Emerging tumor entities and variants of CNS neoplasms. *J Neuropathol Exp Neurol*. 2004 Mar;63(3):185-92
10. Rushing EJ, Thompson LD, Mana H. Malignant transformation of a dysembryoplastic neuroepithelial tumor after radiation and chemotherapy. *Ann Diagn Pathol* 2003 Aug; 7(4):240-4.
11. Perry A, Scheithauer BW, Macaulay RJB, Raffel C, Roth KA, Kros JM. Oligodendrogliomas with neurocytic differentiation. A report of 4 cases with diagnostic and histogenetic implications. *J Neuropathol Exp Neurol* 2002. 61:947-955.
12. Keyvani K, Rickert CH, von Wild K, Paulus W. Rosetted glioneuronal tumor: a case with proliferating neuronal nodules. *Acta Neuropathol* 2001. 101:525-526
13. Hammond RR, Duggal N, Woulfe JM, Girvin JE. Malignant transformation of a dysembryoplastic neuroepithelial tumor. Case report. *J Neurosurg*. 2000 Apr;92(4):722-5.
14. Prayson RA, Abramovich CM. Glioneuronal tumor with neuropil-like islands. *Hum Pathol* 2000. 31:1435-1438.
15. Teo J, Guttekin SH, Bilsky M, Gutin P, Rosenblum MK. A distinctive glioneuronal tumor of the adult cerebrum with neuropil-like (including "rosetted") islands: Report of 4 cases. *Am J Surg Pathol* 1999. 23:502-510.
16. McLendon RE, Bentley RC, Parisi JE, Tien RD, Harrison JC, Tarbell NJ, Billitt AL, Gualtieri RJ, Friedman HS. Malignant supratentorial glial-neuronal neoplasms. Report of two cases and review of the literature. *Arch Pathol Lab Med* 1997. 121:485-492.