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Review of the clinical history and histology
• 49-year-old male with an approximately 18 month history of sinusitis following upper respiratory symptoms with a new episode of sinusitis-like symptoms without antecedent upper respiratory illness which:

  • Did not respond to treatments that previous bouts had, with two antibiotics initiated over a 3 week period with no improvement
  • Also accompanied by increasingly severe headaches which necessitated progressively stronger medications over the same 3 week period,
  • Included new symptoms of irritability, decreased ability to focus, and feeling "foggy”

• CT and subsequent MRI confirmed severe pansinusitis and also demonstrated a solid and cystic rim-enhancing lesion in the right temporal lobe, measuring 6.0 X 5.0 x 4.4 cm
  • Significant associated right-to-left midline shift, and surrounding edema
• Surgical resection was recommended and performed
Smear prep
Touch prep
Frozen Section H&E
Interface of lesion and brain parenchyma, H&E
The best diagnosis in this case is:

Glioblastoma, giant cell variant
General features of glioblastoma

- Hypercellularity
- Anaplastic cytology
- Mitotic activity
- Necrosis and/or endovascular hyperplasia
Intraoperative consultation features
Smear demonstrating glial cytology with anaplasia and atypical mitosis
Touch prep with hypercellularity, anaplasia and mitotic activity
Frozen Section H&E with, in addition to the cytology findings, shows small foci of necrosis
• The necrosis is characterized on the previous slide by tissue breakdown and rare but definite acute inflammatory cells.

• The classic pattern of necrosis associated with glioblastomas is the so-called “pseudopalisading” pattern shown below. This pattern is not required for a diagnosis of glioblastoma.

• Areas of necrosis are surrounded by viable tumor cells that seem to group around or “palisade” around the necrosis.
In some lesions pseudopalisading can be striking, though it is usually not the dominant feature of most glioblastomas, and can often coexist with large areas of geographic necrosis.
• Necrosis must be interpreted with caution if a lesion has been treated with radiation or chemotherapy prior to a resection. In these instances the only pattern of necrosis diagnostic for glioblastoma is the pseudopalisading pattern, as it is not believed to be induced by chemotherapy or radiation.

• This case is an initial resection, so the necrosis contributes to the diagnosis.

• A common companion to necrosis, and having the equivalent ramifications for the grade of the tumor, is endovascular hyperplasia
Endovascular hyperplasia (EVH)

• Vascular proliferation was not a prominent feature of this lesion in either the frozen section or the permanent sections. Although not required, it is somewhat expected to find vascular hyperplasia in the presence of necrosis.

• There is a classic pattern for vascular hyperplasia as well, the glomeruloid pattern. (Named, of course, for its resemblance to the vascular tuft in the glomerulus of the kidneys.)

  • As with necrosis the classic pattern isn’t required. Endovascular hyperplasia can be defined by, and diagnosed in the presence of, the presence of a continuous double (or more) layer of endothelial cells surrounding a microvascular space.
Endovascular hyperplasia:

Classic:

Not classic, but still diagnostic:
Again, in this case endovascular hyperplasia is not appreciated on routine studies.
• And of course a CD34 immunohistochemical study could also highlight the vasculature of the tumor if it was needed to assist in the diagnosis.
  
  • This was not performed, nor was it needed for diagnosis, in this case.

• To round out the diagnosis of glioblastoma, the findings of hypercellularity, anaplasia, mitoses and necrosis were also found on the permanent sections.
Giant cell variant of Glioblastoma

• A variant of glioblastoma with multiple large, bizarre tumor cells.
  • The giant cells often have multiple nuclei, up to 20 or more
    • There is no exact cut off for the proportion of the tumor histology which must be giant cells, sources alternately use “predominant” and “numerous” with accompanying smaller fusiform cells to define the histology
  • Pseudopalisading necrosis is rare in giant cell GBM, more often it is geographic in nature
  • Endovascular hyperplasia is exceptional in giant cell GBM
Geographic necrosis

Abundant giant cells

Abundant variably GFAP positive giant cells

(Giant cells were non-reactive for neurofilament and synaptophysin)
Giant cell GBM clinical features

• The mean age at presentation is 41 years (other primary GBMs present at an average of between 45 and 70 years old)
• Males and females are equally affected
• The preoperative history is usually short
• They are predominantly located in the subcortical temporal and parietal lobes, and can often mimic metastases because of their propensity to be relatively well circumscribed
Giant cell GBM additional features

• GFAP positive, with giant cells having less reliable GFAP positivity
  • Giant cells are nearly always negative for neuronal markers (neurofilament and synaptophysin were used in this case) in contrast to pleomorphic xanthoastrocytoma; the anaplastic variant of pleomorphic xanthoastrocytoma can enter the differential
• Variable presence of a reticulin network around tumor cells
• Occasional perivascular lymphocytic cuffing
• Occasional lipidization of giant cells
• Frequent P53, and PTEN mutations
• EGFR amplification is usually not present
Giant cell GBM genetics

• The general findings in giant cell GBM of common PTEN mutations are paralleled by other primary glioblastomas (33% and 32% respectively)

• The general findings in giant cell GBM of P53 mutations (84%) and rare EGFR amplification (5%) are not shared with most other primary GBMs (P53 rate of 11% and EGFR amplification rate of 39%) and are more reminiscent of secondary GBMs (P53 of 67% and EGFR of 0%)

• This means that giant cell GBM is unique in that it seems to be a hybrid lesion sharing short clinical history, the absence of a less malignant precursor and frequent PTEN mutations with primary GBM, but shares younger patient age at presentation and a high p53 mutation rate with secondary GBM
Molecular markers

- These are starting to be routinely performed on most if not all high grade gliomas to predict response to certain chemotherapeutic agents or to predict prognosis regardless of treatment.

- Some can be performed on paraffin embedded tissue in a semi-quantitative way (p53 which was shown with this case, EGFR, PTEN). However, many of these studies necessitate fresh tissue be frozen at the time of surgery. Usually the best time to do this at UCLA has been with the specimen received for permanent sections - just after a frozen section determination that diagnostic tissue is present.

- The tissue can be frozen at for subsequent studies or to be used in clinical trials, many of which now require fresh frozen tissue for acceptance.
What the molecular markers (might) mean

- Of all the current molecular studies done today, loss of material at 1p/19q is the most robust, with loss of material in both regions nearly rising to a requirement for the diagnosis of oligodendroglioma in an adult.

- EGFRvIII (Epidermal Growth Factor Receptor), PTEN (Phosphatase and Tensin homolog): coexpression of these markers seem to predict response to agents such as erlotinib (Tarceva) and gefitinib.
  - While expression of excess EGFRvIII alone has been associated with a poorer prognosis.

- MGMT (O6-methylguanine-DNA methyltransferase): low levels seem to correspond to increased response to temozolomide.
Prognosis

• Giant cell GBM carries a poor prognosis in general, similar to other glioblastomas

• Some reports have suggested a somewhat better outcome but it is unclear if this is an intrinsic property of the tumor or a result of its propensity to be well circumscribed and therefore more amenable to gross total resection.
To summarize this case, with additional findings:

- Histologic diagnostic features of a relatively well circumscribed, temporal lobe glioblastoma with a large population of variably GFAP positive giant cells – the basis for the diagnosis
  - P53 was not over expressed (an unusual finding in this variant)
  - Reticulin was not found to be abundantly present (an unusual finding in this variant)
  - Electron microscopy showed no evidence of neuronal differentiation (in support of the diagnosis)
  - EGFR was not amplified (in support of the diagnosis)
P53 in this case showing lack of over expression
Reticulin, showing very little staining outside of the tumor vasculature
Electron microscopy showing no evidence of neuronal differentiation (e.g. neurosecretory granules)
The common differentials

• Other GBM
  • Given the unusual genetic profile for giant cell GBM and regions that have only scattered giant cells, this may be a consideration; however, at this time genetics are secondary to histologic, morphologic and radiologic findings which all fit best with giant cell GBM

• Anaplastic pleomorphic xanthoastrocytoma
  • Giant cells lack any evidence of neuronal differentiation, giant cells are positive for GFAP, xanthomatous (lipidized) cells are not present

• Metastasis
  • Unlikely given the morphology of the tumor cells, and almost certainly ruled out by the immunohistochemical studies
References:


• Cavenee, WK. Genetics and new approaches to cancer therapy, Carcinogenesis. 2002;23:683–686


