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Patient:

Hospital No:
Date of Birt
Age/Sex:

Location: 8SIS 8S22

Pathologist: Serguei I. Bannykh, M.D.
Assistant:
Date of Procedure: 4/25/2012
Date Received: 4/25/2012

Accession Number:

Ordering M.D.:
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SURGICAL PATHOLOGY REPORT

********** **Addendum - Please See End of Report** **********

Reason for Addendum #1: Additional studies/stains/opinion(s)

DIAGNOSIS:

A, B. BRAIN, RIGHT FRONTAL, EXCISIONAL BIOPSY:
- **Glioblastoma multiforme, WHO grade IV**

COMMENT:
A high percentage of tumor cells (greater than 20%) immunostaining for MGMT has been reported to be associated with a relatively diminished response to Temodar (Friedman et al., J Clin Onc 16: 3851-3857; 1998). Hence, the low 1% result in this case suggests a likelihood of this tumor being responsive to Temodar.

Inactivating mutations in isocitrate dehydrogenase (IDH) I and II (R132H and R172K respectively) have been found to be an independent favorable prognostic marker in infiltrating gliomas (Yan et al. *IDH1* and *IDH2* Mutations in Gliomas. N Engl J Med 2009;360:765-73).

Recent studies have shown that co-expression of EGFRvIII and PTEN as detected by immunostaining was significantly correlated with a clinical response of glioblastomas to EGFR kinase inhibitors (N Engl J Med. 353(19):2012-24; 2005). Hence the preserved expression of PTEN in this case, when combined with EGFRvIII mutation, permits a possibility of this tumor being responsive to EGFR-kinase inhibitors.

Retained expression of PTEN was found to be associated with a more favorable prognosis in patients with high grade gliomas (Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, Misra A, Nigro JM, Colman H, Soroceanu L, Williams PM, Modrusan Z, Feuerstein BG, Aldape K. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell. 2006 9(3):157-73).

Recent studies indicated an adverse prognostic significance of increased expression of laminin beta 1 and decreased expression of laminin beta 2 predicting a worse survival of patients with gliomas. (Ljubimova JY. Association between laminin-8 and glial tumor grade, recurrence, and patient survival. Cancer. 2004 Aug 1;101(3):604-12).
Accordingly, elevated expression of beta 1 and suppressed expression of beta 2 in this tumor predict more aggressive behavior.

Presence of activated (phosphorylated) p42/44 Mitogen-Activated Protein Kinase (pMAPK) often is indicative of an upregulation of receptor tyrosine kinase signaling. It has been shown to be associated with a relative resistance to radiation therapy in glioblastoma multiforme (Pelloski et al. 2006. Prognostic Associations of Activated Mitogen-Activated Protein Kinase and Akt Pathways in Glioblastoma. Clin Cancer Res. 2006;12(13): 3935-3941).
Correspondingly, a high percentage of tumor cells immunoreactive to pMAPK antibody in this case may predict a relative resistance to radiation therapy.

The use of these tests in guiding therapy has limitations. Review of the relevant literature and clinical correlation is advised. These test results do not obligate or preclude use of the relevant therapeutic agents.

HISTORY:
Frontal mass

MICROSCOPIC FINDINGS:
Sections disclose infiltrative glioma composed of pleomorphic tumor cells of various morphologies. Some of the tumor nuclei are highly pleomorphic enlarged and show atypical mitotic figures whereas others are small and often aggregate to impart a small cell morphology to large areas of the tumor. Extensive endothelial proliferation and foci of palisading tumor necrosis are identified. No apparent differentiation from an ependymoma is seen in this cystic tumor. Given the young age of the patient a possibility of this tumor originating in a background of genetic predisposition syndrome was evaluated using antibody to p53 and to mismatch repair enzymes.

IMMUNOHISTOCHEMISTRY:

Study / Antibody	Block	Result
P53 QL	B2	up to 90% of tumor cells are positive (2-3+)
Isocitrate Dehydrogenase-1R132H mutant	B2	Positive in 20% of cells
MGMT QT, man	B2	Less than 1% of tumor nuclei is positive
PTEN QT, man	B2	Retained (2-3+)
P44/42 MAPK QT, man	B2	Up to 90% of tumor nuclei and cytoplasm is positive
Laminin Beta 1 QT, man (8/411)	B2	Up-regulated (3+)
Laminin Beta 2 QT, man (9/421)	B2	Focally down-regulated (0-1+)
MSH-2 QL	B2	Retained expression
MSH-6 QL	B2	Retained expression
PMS2 QL	B2	Retained expression
MLH-1 QL	B2	Retained expression
EGFR by FISH	B2	Pending

*These IHC studies were interpreted in conjunction with appropriate positive and negative controls which demonstrated the expected positive and negative reactivity.

GROSS:
A. RIGHT FRONTAL BRAIN MASS FROZEN
Labeled designated "right frontal brain mass", and received fresh for intraoperative consultation are several fragments of pink-tan soft tissue measuring 0.5 cm in greatest aggregate dimension. Half of the fragments are submitted for frozen section, and further submitted for permanent sections in block A1. The remaining tissue is submitted in block A2.
A1. Frozen section remnant - multiple
A2. Remaining tissue - multiple

B. RIGHT FRONTAL BRAIN MASS
Labeled designated "right frontal brain mass", and received in formalin is an aggregate of soft friable pink-tan to white soft tissue measuring 4.2 x 2.5 x 0.8 cm in aggregate. Entirely submitted.
Slide key:
B1-B4. Multiple each

Gross dictated by Shawn Maclary, P.A.(ASCP):mrs (913475)
04/25/12

INTRAOPERATIVE CONSULTATION:
OPERATIVE CALL
OPERATIVE CONSULT (FROZEN AND TP):

FSA/TPA: BRAIN, RIGHT FRONTAL:
- Glioma
(Serguei Bannykh, M.D.)
amc/04/26/12/J#913948

I have personally examined the specimen, interpreted the results, reviewed the report and signed it electronically.
Serguei I. Bannykh, M.D. Electronically signed 4/26/2012 6:07:37PM

FLUORESCENCE IN SITU HYBRIDIZATION (FISH) for EGFR in BRAIN

Tissue Block: B2

RESULTS: **NORMAL** EGFR & chromosome 7 signal pattern

Number of cells evaluated: 40

INTERPRETATION:
Fluorescence in situ hybridization (FISH) analysis on a brain tumor sample from this patient with Abbott Molecular probes specific for the centromere of chromosome 7 (control probe) and the short arm (EGFR-7p12) of chromosome 7 was performed. The control sample gave expected results.

These studies did not detect any aberrant signal patterns of EGFR in the 40 nuclei examined, with an EGFR gene to Cep 7 signal ratio of 1.1

NOTE:
Samples are considered positive in brain if the EGFR to CEP 7 signal ratio is ≥ 2.0 in ≥ 10% of analyzed cells or tumors with four or more copies of the EGFR gene in ≥ 40% of the cells (high polysomy).

References:
Hirsch, FR. Et al. (2005) J Clin Concol Vol 23(28), pp.6838-45
Dziadziuszko et al. (2006) Clin Cancer Res. Vol 12(14 Suppl), pp.4409s-4415s
Hirsch et al. (2008) J Clin Oncol Vol 26(20), pp3351-3357

These FISH tests were developed and their performance characteristics determined by CSMC Cytogenetics Laboratory as required by the CLIA '88 regulations. They have not been cleared or approved for specific uses by the U.S. Food and Drug Administration.

I have personally examined the specimen, interpreted the results, reviewed the report and signed it electronically.
Jean Lopategui, M.D. Electronically signed 4/27/2012 5:27:34PM
Serguei I. Bannykh, M.D. Electronically signed 4/27/2012 6:21:46PM