Diagnostic Approaches to Glioblastoma Subtypes and Histologic Patterns: How have we changed our thinking?

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Case-Based Questions (please see page 4 for answers)

1.	A 65-year-old patient presented for neurosurgical resection of a non-contrast-enhancing frontal lobe brain mass. Histopathology showed a hypercellular diffuse glioma composed of cells with small, uniform, slightly oval nuclei without discernable cytoplasm, and frequent mitotic figures. Vascular proliferation and necrosis were present only focally. The tumor cells were positive for GFAP and OLIG2, and negative for synaptophysin. IDH1 R132H immunohistochemistry was negative, and ATRX was positive (retained). Which of the following genetic alterations is most likely to be identified in this tumor?	
	a.	BRAF p.V600E mutation
	b.	EGFR amplification
	c.	FGFR3::TACC3 fusion
	d.	NF1 inactivating mutation
	e.	MYC amplification

2.	A 5-year-old patient presented for neurosurgical resection of a cortically-based contrast-enhancing parietal lobe mass. Histopathology showed a malignant glioma containing markedly enlarged cells with bizarrely-shaped, irregular nuclei and frequent multinucleated giant cells. There was a positive family history of cancer on both the maternal and paternal sides. Germline testing for which gene(s)/syndrome is indicated?	
	a.	CDKN2A, melanoma-astrocytoma syndrome
	b.	DICER1, DICER1-related tumor predisposition syndrome
	c.	MLH1, PMS2, MSH2, MSH6, constitutional mismatch repair deficiency (CMMRD)
	d.	NF1, neurofibromatosis type 1
	e.	TP53, Li-Fraumeni syndrome

3.	Histopathology following resection of a ring-enhancing occipital lobe brain mass in a 72-year-old patient identified a diffuse astrocytic glioma with cytologic anaplasia, mitotic activity, palisading necrosis, and microvascular proliferation. The tumor cells were negative for IDH1 p.R132H mutant protein and were positive (retained) for ATRX. Some regions of the tumor showed markedly increased hypercellularity, nuclear molding, >90% Ki67 labeling index, loss of immunoreactivity for GFAP and OLIG2, and positivity for synaptophysin. Molecular testing identified MYCN amplification, among other alterations. What additional testing should be considered?	
	a.	Body imaging for extra-cranial metastatic disease
	b.	Craniospinal imaging for cerebrospinal fluid dissemination
	c.	Molecular testing for FGFR3::TACC3 fusion
	d.	Screening for Lynch syndrome

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Correct Answers and Rationales

Question 1 Correct Answer and Rationale: **B. EGFR amplification**

Rationale: The case describes the histopathologic features of small cell glioblastoma, which has a high frequency of EGFR activating alterations including gene amplification and the EGFR-vIII splice variant. About one-third of these tumors are non-contrast-enhancing and may lack microvascular proliferation or necrosis in microscopic evaluation. Within the context of glioblastoma subtypes and patterns, FGFR3::TACC3 fusion is associated with glioblastoma with oligodendroglioma-like features. BRAF p.V600E mutation is associated with epithelioid glioblastoma. NF1 inactivating mutations are associated with gliosarcoma. MYC amplification is associated with glioblastoma with primitive neuronal component.

Question 2 Correct Answer and Rationale: **C. MLH1, PMS2, MSH2, MSH6, constitutional mismatch repair deficiency (CMMRD)**

Rationale: The young patient age, positive family history of cancer, and described histomorphology aligning to giant cell glioblastoma all suggest an inherited DNA mismatch repair deficiency. Biallelic germline alterations of MSH2, MSH6, MLH1, PMS2 are reported. Although not all giant cell glioblastomas have a germline or somatic DNA mismatch repair defect, the finding of giant cell features or the giant cell glioblastoma subtype raises this possibility and may prompt immunohistochemical testing for the DNA mismatch repair proteins and/or DNA sequencing studies. Melanoma-astrocytoma syndrome, caused by germline disruption of the CDKN2A tumor suppressor gene, is associated with several astrocytoma types/subtypes that are not histopathologically distinguished from their corresponding sporadic forms. Patients with DICER1-related tumor predisposition syndrome are predisposed to several tumor types including primary intracranial sarcoma, DICER1-mutant, which can be a differential consideration for gliosarcoma. Giant cell features in a high-grade glioma are less common in neurofibromatosis type 1 and Li-Fraumeni syndrome patients, compared to CMMRD.

Question 3 Correct Answer and Rationale: **B. Craniospinal imaging for cerebrospinal fluid dissemination**

Rationale: The histopathologic features align with glioblastoma with primitive neuronal component, which has a high rate of cerebrospinal fluid dissemination. Amplification of MYC or MYCN is identified in about 40% of cases. Studies on extra-cranial metastatic disease from glioblastoma have suggested an increased rate for gliosarcoma. FGFR3::TACC3 fusion-positive glioblastomas may show oligodendroglioma-like features. Glioblastomas occurring in the setting of a DNA mismatch repair syndrome, such as Lynch syndrome, CMMRD, or polymerase proofreading-associated polyposis syndrome (caused by mutations in POLE and POLD1) may contain giant cells and align in some cases to giant cell glioblastoma.