Hereditary Tumor Syndromes

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Case-Based Questions (please see page 3 for answers)

1.	A 6-year old boy presents with a ring-enhancing mass in the left frontal lobe. Histology shows a high-grade diffuse glioma with numerous giant cells. Further clinical workup shows that the patient has café-au-lait macules, but no neurofibromas and that the parents are first cousins. This patient most likely suffers from which hereditary tumor syndrome?	
	a.	Neurofibromatosis type 1 (NF1)
	b.	Cowden disease
	c.	Von Hippel-Lindau disease
	d.	Constitutional mismatch repair defect (CMMRD) syndrome
	e.	Tuberous sclerosis complex

2.	A 21-year old woman develops two separate schwannomas involving the right ulnar nerve. Which histologic finding would further favor an underlying schwannomatosis?	
	a.	A mosaic pattern of INI1 staining
	b.	Loss of MLH1 staining in tumor nuclei, but retained expression in endothelial cells
	c.	Strong and diffuse p53 immunoreactivity
	d.	GAB1 expression in tumor cells
	e.	Loss of PRKAR1A expression in tumor cells

3.	A 36-year old man with known NF1 undergoes removal of a plexiform neurofibroma that has recently been growing. The histopathology is most consistent with atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP). Which immunohistochemicl result further supports this diagnosis?	
	a.	Extensive p53 positivity.
	b.	Loss of H3K27me3 expression.
	c.	Loss of p16 staining in tumor cells.
	d.	Lack of S100 staining in tumor cells.
	e.	Desmin positivity in a subset of tumor cells.

Scroll to Page 3 for answers

Question 1 Correct answer and rationale: **D) Constitutional mismatch repair defect (CMMRD) syndrome**

Although café-au-lait macules are also commonly encountered in NF1 and high-grade gliomas may also be seen in that syndrome, the parental consanguinity and lack of neurofibromas strongly favors CMMRD syndrome. The other 3 syndromes do not predispose patients to high-grade gliomas.

Question 2 Correct answer and rationale: **A) A mosaic pattern of INI1 staining**

A mosaic pattern of INI1 staining (i.e., with loss of expression in only a subset of tumor nuclei) is commonly seen in schwannomas of patients with either schwannomatosis or NF2. None of the other findings would be common in schwannomas. In the appropriate settings, loss of MLH1 expression in tumor cells suggests Lynch syndrome, extensive p53 positivity is seen in Li-Fraumeni syndrome, GAB1 staining reflects SHH activation, and loss of PRKAR1A expression is seen in a subset of tumors in Carney Complex.

Question 3 Correct answer and rationale: **C) Loss of p16 staining in tumor cells.**

A premalignant or early malignant event in the transformation of NF1-associated neurofibromas is CDKN2A inactivation, which leads to the loss of p16 expression in the tumor cells of ANNUBP. All of the other results listed are much more common in MPNST, including heterologous myogenic differentiation with desmin staining.