Peripheral Nerve Sheath Tumors in Neurofibromatosis

Anat Stemmer-Rachamimov, MD

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

1.	A 20-year-old man has multiple benign nerve sheath tumors arising bilaterally with hybrid schwannoma/neurofibroma features. There is no family history of neurofibromatoses and there is no evidence of skin lesions. MRI (thin slice) shows no evidence of vestibular schwannomas. Which of the following statements is true?	
	a.	The patient cannot have NF2 because he has no vestibular schwannomas
	b.	The patient cannot have NF1 because he has no café au lait spots, freckles of cutaneous neurofibromas
	c.	The patient has schwannomatosis because there are no other lesions or family history
	d.	The differential diagnosis includes all forms of NF: NF1, NF2 and schwannomatosis

2.	The patient's tumor is a plexiform tumor with hybrid features of schwannoma and neurofibroma. Which of the following panels of stains will be helpful for the diagnosis:	
	a.	P53, p16, H3K27me3, S100
	b.	Ki67, IDH1, ATRX,
	c.	S100 or SOX 10, CD34, Glut1 or EMA, Neurofilament, SMA
	d.	S100, SSTR2A, progesterone receptor, EMA

3.	The tumor staining pattern supports the diagnosis of a neurofibroma. Which of the following is diagnostic of malignant transformation?	
	a.	Necrosis of complete loss of H3K27me3 expression
	b.	Areas of increased cellularity
	c.	Scattered large, hyperchromatic nuclei
	d.	Infiltrative margins

Scroll to Page 3 for answers

Question 1 Correct answer and rationale: **D) The differential diagnosis includes all forms of NF: NF1, NF2 and schwannomatosis**

The patient can have NF2 and may develop vestibular schwannomas later, often by age 30. Some forms of NF2 will have vestibular schwannomas only later in life or in cases of mosaic NF2 may not have vestibular schwannomas at all. Manifestations of NF1 vary greatly and there is a form in which only spinal nerves are involved. Spinal NF1 is a subset of NF1 in which patients do not have the classic clinical symptoms. In some families, the underlying NF1 mutations were found to cause reduced neurofibromin in cells but no truncated proteins. These findings may explain why the phenotype is different from classic NF1 in which truncated proteins are present. Lack of family history is not unusual in NF1 or NF2; as 50% of the cases are de nuovo mutations. The patient may have schwannomatosis but the diagnosis would require confirmation by molecular information (germline mutation).

Question 2 Correct answer and rationale: **C) S100 or SOX 10, CD34, Glut1 or EMA, Neurofilament, SMA**

The most useful panel of stains to distinguish between a neurofibroma and a schwannoma includes S100 (which highlights Schwann cells), CD34 (fibroblasts), Glut1 or EMA (perineurial cells), neurofilament (axons) and SMA (myofibroblasts). In Schwannomas, the great majority of the cells will be S100 positive, not only in the compact or cellular areas, but also in the loose, neurofibroma like areas. If there will be axons those will be mostly confined to the periphery of the tumor. On the other hand, a neurofibroma is composed of multiple cell types, so the composition of the tumor in the loose (neurofibroma like) areas will be mixed. Entrapped axons, splayed apart by tumor, in the center of the tumor are more typical of a neurofibroma.

Question 3 Correct answer and rationale: **A) Necrosis of complete loss of H3K27me3 expression**

Necrosis or loss of H3K27me3 expression are diagnostic of an MPNST. Other features such as isolated increased cellularity (cellular neurofibroma) or scattered atypical nuclei, are not indicative of malignant transformation when isolated. The presence of 2 atypical features is sufficient for the diagnosis of an atypical neurofibromatous neoplasm with unknown biological potential (ANNUBP).