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Immunohistochemistry

Immunohistochemistry in the Differential Diagnosis of Schwannoma and Neurofibroma

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When they present with classic morphologic features, schwannoma and neurofibroma can be recognized with confidence based on H&E. However, as most pathologists know, tumors do not read textbooks, and as a result the differential diagnosis between these tumors can be a challenge. Although in many cases this distinction may be only of academic interest, because of the association of neurofibroma with certain hereditary syndromes, there are situations where the distinction of schwannoma from neurofibroma can be of some clinical importance. This month, we briefly discuss several immunostains that can be of utility in assisting with this differential diagnosis.

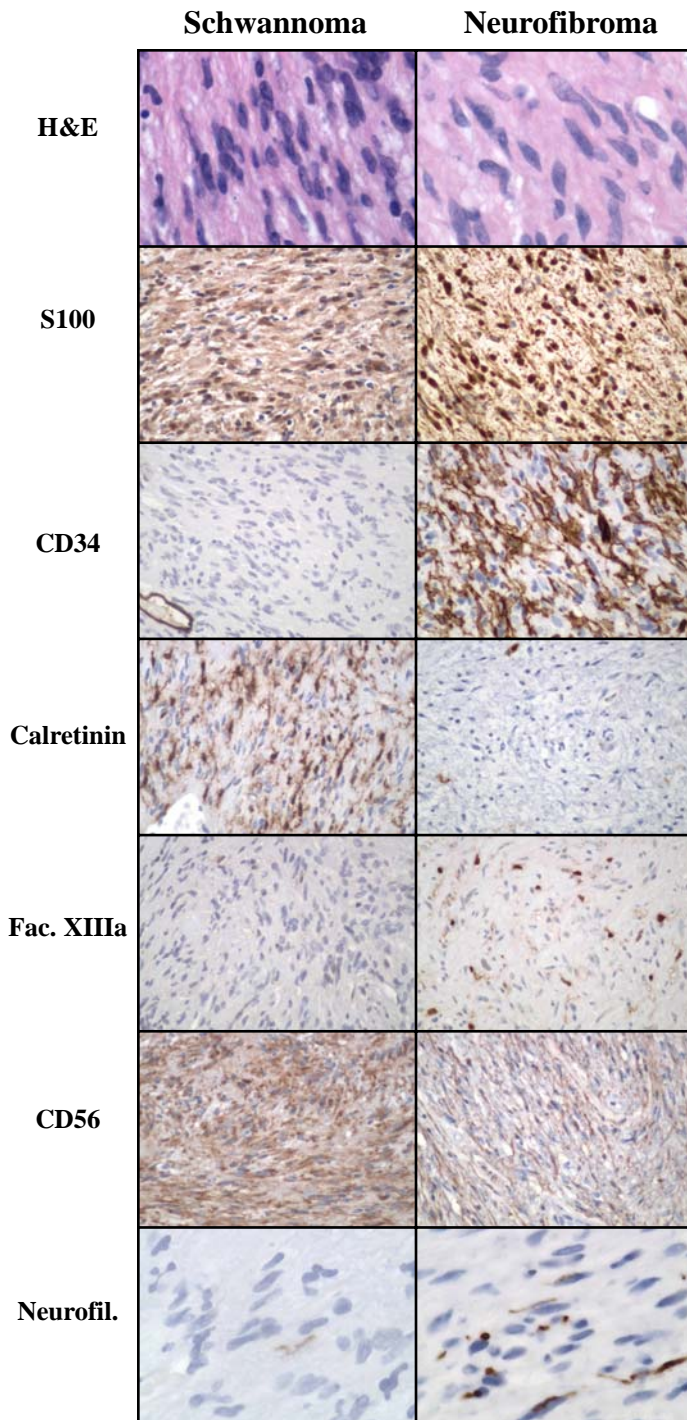
S100 protein is undoubtedly the first immunostain people think of when these tumors come to mind, since they both arise from peripheral nerves, which have been known to strongly express S100 for many years. There is some truth to the contention that schwannomas express S100 to a greater extent than neurofibromas, but because of a degree of overlap in the expression of this marker between these two tumors, relying on this stain alone is not sufficient. However, I virtually always order S100 when these differential diagnostic possibilities come to mind, since all neurofibromas and schwannomas show moderate to strong expression of this marker, and its absence in a case of suspected schwannoma or neurofibroma should make the pathologist consider other diagnostic possibilities.

CD34 is a useful stain for this differential diagnosis, since neurofibromas typically demonstrate a significant subpopulation of CD34-positive stromal cells, unlike most schwannomas. However, some authors describe a minor population of CD34-positive cells that may occur in the noncellular (Antoni B) areas of some schwannomas, although I have not yet personally observed this finding. Undoubtedly, this reflects the fact that schwannoma is considered to be a tumor composed of schwann

cells and little else, whereas neurofibromas contain additional cellular components (endoneurial fibroblasts, perineurial-like cells, etc) that are responsible for this CD34 reactivity. As expected, blood vessels present in both tumors stain strongly with CD34.

At the March 2004 United States and Canadian Academy of Pathology meeting, Fine and colleagues reported on their studies using **calretinin** as an aid to distinguish neurofibromas from schwannomas (subsequently published in the October 2004 American Journal of Clinical Pathology). As expected, calretinin strongly labels mast cells in both schwannoma and neurofibroma, but when taking background mast cells into account, the authors noted a marked difference in calretinin reactivity between schwannomas and neurofibromas. Their study included 25 schwannomas, and 24 of those tumors (96%) showed moderate to strong staining for calretinin, which occurred in either a focal or diffuse fashion. The one calretinin-negative schwannoma arose from the stomach. In their discussion, the authors noted that studies have shown a markedly decreased frequency of NF2 mutations in GI schwannomas (compared to soft tissue schwannomas), raising the possibility that the underlying genetic mechanisms leading to GI schwannomas might be different than those leading to soft tissue schwannomas. In contrast, only 3 of 42 neurofibromas (7%) demonstrated staining with calretinin. Those that did stain demonstrated weak to moderate staining in less than 25% of the tumor cells.

Other markers that may be of some utility include **Factor XIIIa** (reportedly positive in neurofibroma but negative in schwannoma), and **CD56** (reportedly negative in neurofibroma and positive in schwannoma, although I have seen focal CD56 in a plexiform neurofibroma). We have also evaluated **neurofilament** in a number of these types of cases, and I have observed neurofilament in both tumors, although positive cells often



<u>Antibody</u>	<u>Schwannoma</u>	<u>Neurofibroma</u>
S100	++++ (nearly every cell +)	++ to ++++
CD34	- / focal +	++ to +++
Calretinin	++ to +++ (can be focal)	- (7% focal+)
Factor XIIIa	- or few + cells	++
CD56	++ to +++	- to +
Neurofilament	- to rare +	few + to ++

requires high power search. Because of the fact that neurofibromas grow within and may envelop the nerve of origin (as opposed to schwannomas which displace the nerve of origin), neurofilament can allow you to see entrapped background nerve remnants in neurofibroma (that are not present in schwannoma, except occasionally on the very periphery of the lesion). If any questions arise about the benign vs. malignant nature of the lesion in question, I find **Ki-67** very helpful, which shows a low proliferative fraction in the benign lesions.

In summary, the differential diagnosis of schwannoma versus neurofibroma should be possible by employing

immunostains to S100 protein (which should be positive in all cases), CD34, and calretinin. Factor XIIIa, neurofilament, and CD56 may also be of some help. Alas, despite our hopes to the contrary, we still see occasional cases where the distinction between schwannoma and neurofibroma is still difficult, even with the benefit of a tray of immunostains. Perhaps these cases represent tumors with hybrid features.

Expected staining results in most cases are listed above.

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