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Immunohistochemistry Division

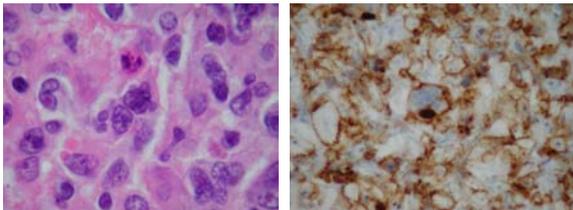
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Focus on Immunohistochemistry - August 2001 CD56 (NCAM)

CD56, also known as neural cell adhesion molecule (NCAM), was originally identified in the nervous system, and belongs to a group of cell adhesion molecules including cadherins, selectins, and integrins. CD56 was subsequently found to be present in a number of non-neural tissues. The development of antibodies capable of recognizing CD56 in paraffin sections has contributed to the increased recognition of certain lymphomas, neuroendocrine and neural tumors, and also certain mesenchymal tumors.

CD56 in lymphohematopoietic neoplasms

CD56 has found great utility in the recognition of natural killer (NK) and NK/T-cell lymphomas in paraffin section material. CD56 is characteristically positive in nasal and nasal-type NK/T-cell lymphomas, and it is also positive in aggressive NK cell leukemia and blastic NK leukemia/lymphoma. NK/T-cell lymphomas are probably most commonly recognized in the sinonasal tract, where they have a tendency to show angiocentric growth, and are often associated with extensive necrosis. Nasal NK/T-cell lymphomas characteristically are negative for surface



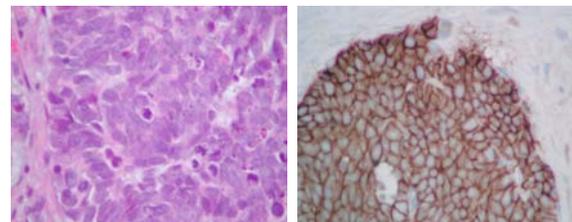
Liver biopsy on 53-year-old male presenting with multiple liver and kidney nodules. Flow cytometry was nondiagnostic, but immunohistochemistry showed features of NK/T cell lymphoma of nasal type. CD56 immunostain is shown on the right. Cytoplasmic CD3 was positive, but CD5 and CD7 were negative

CD3 although they express cytoplasmic CD3 (which is detectable by the common polyclonal CD3 antibody used in paraffin section material). They are usually negative with the pan-T-cell markers CD5 and CD7, and express EBER in greater than 90% of cases. Because of their expression of cytoplasmic CD3, these lymphomas might be

interpreted as T-cell lymphomas if only CD3 is used as a single T-cell marker. Therefore, it is reasonable to routinely apply an additional pan-T-cell marker (like CD5) when working up lymphoma cases. If one is faced with a CD3 positive tumor (in paraffin sections) that is negative for both CD5 and CD7, a CD56-positive NK/T-cell lymphoma is high on the list of diagnostic possibilities. In addition to the previously-mentioned entities, CD56 is also expressed in a subset of peripheral T-cell lymphomas, and may also be expressed in some cases of lymphoblastic lymphoma, anaplastic large cell lymphoma, acute myeloid leukemia, and some cases of T-cell CLL/PLL. At the 2001 U.S. and Canadian Academy of Pathology meeting in Atlanta, Knowles and colleagues reported on their studies of CD56 expression in plasma cell lesions (abstract # 949). They noted that CD56 was negative or weak in benign plasma cells, but was positive in 71% of myelomas. CD56 was positive in only 7% of monoclonal gammopathies of undetermined significance. Of the CD56 positive cases of myeloma, 89% were associated with bone lesions. They also found that in anaplastic plasmacytoma and extramedullary plasmacytoma, CD56 expression was not observed, and plasma cells associated with lymphoplasmacytoid lymphomas were also CD56 negative.

CD56 in neuroendocrine and neural tumors

CD56 is commonly expressed (in a membrane pattern) in neuroendocrine neoplasms. It is not as specific for neuroendocrine differentiation as chromogranin and synaptophysin, but in the case of small cell carcinoma, it has higher sensitivity. For that reason, we always include

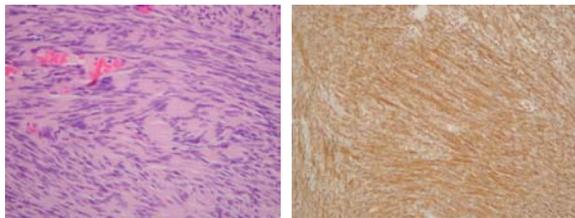


Small cell carcinoma of lung expressing CD56 (right).

CD56 as part of our small cell carcinoma panel. Although we are able to demonstrate either chromogranin or synaptophysin in >90% of the small cell carcinomas that we see at ProPath, the expression of chromogranin and synaptophysin may be quite weak, and CD56 is generally much more strongly expressed in small cell carcinoma. CD56 is much less common in non-neuroendocrine tumors of pulmonary origin.

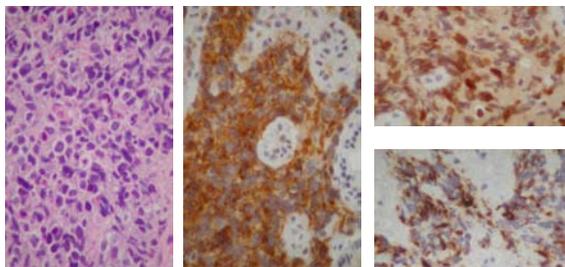
CD56 in mesenchymal tumors.

Miettinen et al reported on a series of mesenchymal neoplasms stained with CD56 at the 2001 United States and Canadian Academy of Pathology in Atlanta (abstract #72). Mesenchymal tumors that show a high frequency of expression of CD56 included schwannoma, paraganglioma, pheochromocytoma, ganglioneuroma, ganglioneuroblastoma, neuroblastoma, synovial sarcoma, alveolar rhabdomyosarcoma, uterine leiomyoma, embryonal rhabdomyosarcoma, and meningioma. Variable expression was identified in malignant peripheral nerve sheath tumor, melanoma, leiomyosarcoma, GIST, chordoma, Ewing's sarcoma, and epithelioid sarcoma. The follow-



Schwannoma showing expression of CD56 (right).

ing mesenchymal neoplasms were negative for CD56: neurofibroma, granular cell tumor, solitary fibrous tumor, juvenile fibromatosis, vascular leiomyoma, fibrous histiocytoma, DFSP, and angiosarcoma. Based on the above reports, we have found CD56 to be of utility in separating cases of schwannoma vs. neurofibroma (although we have observed CD56 expression in the plexiform areas of



H&E section (left) of destructive nasal tumor in 81-year-old female. Initially the strongly positive CD56 stain (center) led to consideration of NK/T-cell lymphoma, but CD45 and CD3 were negative. Subsequent immunostains showed strong expression of myogenin (top right) and neurofilament (bottom right), indicating that the tumor was a polyphenotypic small round cell tumor with divergent differentiation (rhabdomyosarcomatous and neural). All epithelial markers were negative.

plexiform neurofibroma), and have also identified cases where strong CD56 expression has pointed us toward identifying rhabdomyosarcoma in a tumor that otherwise had morphologic features more typical of lymphoma (illustrated above).

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