PROPATH
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Immunohistochemistry

Calretinin

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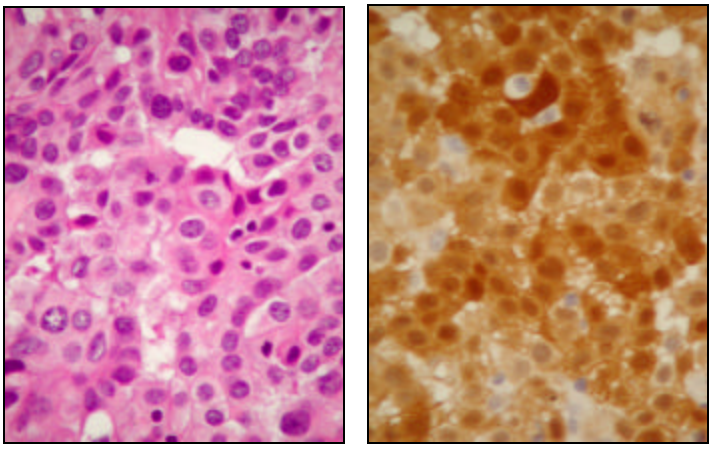
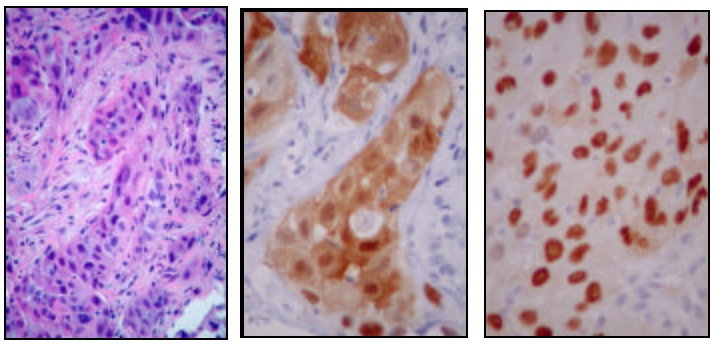
Calretinin is undoubtedly best known as a “positive” marker of mesothelioma. It is reported to stain a very high percentage (>95%) of epithelioid mesotheliomas, and staining of both nuclei and cytoplasm should be observed. However, it is not uncommon for sarcomatous mesotheliomas to lack this marker. Unfortunately, we all know that there are no "perfect" markers, and calretinin is no exception. When employing this marker in the differential diagnosis of mesothelioma vs. carcinoma, it is important to be aware of the spectrum of calretinin immunoreactivity that may be observed in tumors that may mimic mesothelioma, particularly when dealing with small biopsy specimens (which seem to be getting progressively smaller every year). **Pulmonary squamous carcinomas** may express strong and diffuse calretinin, an observation to my knowledge first reported in a 1998 study by Ordonez evaluating calretinin reactivity in a large series of carcinomas metastatic to the pleura. In that study, he found expression of calretinin in 11 of 28 (40%) of pulmonary squamous carcinomas. This is an important point to keep in mind, particularly since another commonly used "positive" marker of mesothelioma, cytokeratin 5/6, is also strongly expressed in squamous carcinomas (although mesotheliomas do not express p63, which is typically expressed in most squamous tumors). Ordonez identified weak or focal calretinin reactivity in 3 of 38 (8%) pulmonary adenocarcinomas, 5 of 38 (13%) ovarian carcinomas, 2 of 15 (13%) endometrial carcinomas, 2 of 23 (9%) breast carcinomas, and 2 of 16 (13%) colonic carcinomas, but did not find any reactivity in prostate carcinoma (n = 8), thyroid carcinoma (n = 6), large cell undifferentiated carcinoma of the lung (n = 8), and transitional cell carcinoma (n = 9). (Parenthetically, I should mention that at ProPath, we have seen strong calretinin reactivity in several urothelial carcinomas). In this month's issue of the American Journal of Surgical Pathology, Miettinen and Sarlomo-Rikala report a study of 596 lung carcinomas immunostained with calretinin and several other mesothelioma markers. They found calretinin expression in 67% of giant cell carcinomas, 49% of small cell carcinomas, and 38% of large cell carcinomas. 11% of adenocarcinomas and 17% of carcinomas with neuroendocrine differentiation expressed calretinin in their study. These and similar studies in the literature underscore the importance of using appropriate **panels of immunostains** to approach diagnostic problems.



H&E (left) of tumor in cervical node biopsy from a 57 year old male with no known primary tumor. A battery of immunostains including calretinin (right) was diagnostic of mesothelioma, and subsequent workup revealed the pleural primary. Note that both nuclei and cytoplasm stain with calretinin.

Calretinin has also found utility in the diagnosis of **adrenocortical tumors**. In a 2002 study of 33 adrenocortical tumors, Jorda et al found that inhibin was expressed in 73% of the adrenocortical neoplasms, but when calretinin was added, positivity for the two markers alone or in combination increased to 94% of adrenocor-



H&E (left) of needle biopsy of pleural mass on 68 year-old male. Strong, diffuse calretinin was noted (middle), and there was intense expression of cytokeratin 5/6. However, the tumor cells showed strong nuclear staining with p63 (right), pointing to a squamous origin, and the tumor also expressed other markers (strong CEA and MOC31) that excluded mesothelioma. This case represents a ***calretinin-positive squamous carcinomna***.

tical tumors. Staining was focal in many of the cases. Because of the substantial increase in sensitivity, the authors advocate using both calretinin and inhibin when trying to diagnose adrenocortical neoplasms. (Parenthetically, in this situation I also employ MART-1 clone A103, as we have also seen that marker stain some adrenal cortical neoplasms that have not expressed inhibin.) Calretinin is also useful in the diagnosis of **ovarian sex-cord stromal tumors**. In a 2002 study from Johns Hopkins, calretinin reactivity was found in 100% of 87 ovarian sex cord stromal tumors of various types and 90% of 37 fibrous neoplasms (including 32 that were inhibin negative). Calretinin staining was noted in 22% of 65 epithelial tumors, but in none of 22 germ cell tumors. Not surprisingly, calretinin also has been found to be a useful marker in **Leydig cell tumors of the testis**.

A number of other tumors have also been found to express calretinin. In a 2001 paper, Miettinen and co-workers found fields or areas of calretinin positive tumor cells in 71% of 41 biphasic **synovial sarcomas**, 52% of monophasic synovial sarcoma, and 56% of poorly differentiated synovial sarcomas. 2 of 15 malignant peripheral sheath tumors showed focal reactivity, but epithelioid sarcomas, leiomyosarcomas, GIST's, and angiosarcomas were negative. (Parenthetically, I have not found calretinin to have major diagnostic utility in the diagnosis of synovial sarcomas at ProPath). **Granular cell tumors** express this marker, as indicated by a paper in this month's issue of the American Journal of Clinical Pathology. In that study, 93% of 43 granular cell tumors were positive for calretinin, although the degree of reactivity varied substantially from focal weak staining to diffuse strong staining. They also noted increased staining of tumor cells adjacent to the overlying hyperplastic squamous epithelium. As expected, all tumors were positive for S100, and they also expressed inhibin, with greater than half of the cells showing moderate to strong staining. Calretinin is also present in **mast cell lesions**, although in view of the excellent sensitivity and specificity of mast cell tryptase, calretinin would have to be considered a second line marker for those lesions. For those of you who read and retain the abstracts from the United States and Canadian Academy of Pathology meetings, abstract # 386 from the 2001 meeting (published in the January 2001 issue of Modern Pathology) reports a study of calretinin in cutaneous tumors, and abstract # 878 describes calretinin reactivity in a study of mesenchymal and neuroendocrine tumors.

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