

## Differential Diagnosis of Cytokeratin “Dots”

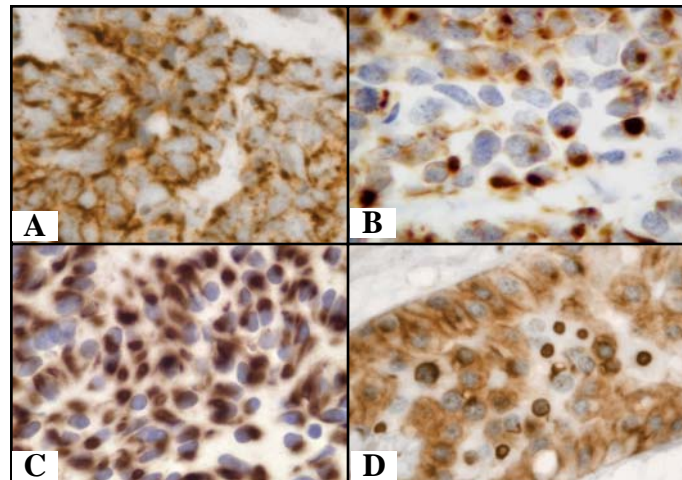
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In addition to evaluating the presence or absence of immunoreactivity per se, identification of a particular pattern of immunoreactivity is important, and can provide significant diagnostic information. One such pattern is perinuclear immunoreactivity, usually in the form of intracytoplasmic perinuclear dots or globs. This month, we direct our attention to the types of tumors that may show this perinuclear pattern of reactivity with cytokeratin antibodies.

Undoubtedly the most common tumor demonstrating perinuclear cytokeratin dots is **small cell carcinoma**. Typically in this tumor, the dots are relatively small, and in nearly all cases, these cytokeratin dots are more prominent with low molecular weight cytokeratin than with high molecular weight cytokeratin. This pattern of reactivity is so characteristic of small cell carcinoma that I am hesitant to render that diagnosis in the absence of this pattern of cytokeratin reactivity.

**Other neuroendocrine tumors** also commonly show perinuclear cytokeratin immunoreactivity. **Merkel cell tumor** (high-grade primary cutaneous neuroendocrine carcinoma) nearly always shows perinuclear cytokeratin reactivity, and the appearance of the perinuclear cytokeratin deposits in Merkel cell tumor is more akin to "globs" than dots, secondary to their larger size. In fact, the large size of these perinuclear cytokeratin globs can be a helpful clue to the diagnosis. Indeed, in several personally-observed cases presenting with metastatic disease, this clue (i.e., large intracytoplasmic perinuclear cytokeratin globs) eventually led to the correct diagnosis of Merkel cell tumor in these cases, that



A: Cytokeratin LMW stain on small cell carcinoma. B: Cytokeratin 20 stain on Merkel cell tumor. C: Cytokeratin LMW stain on gastric carcinoid tumor. D: Cytokeratin LMW stain on renal oncocytoma.

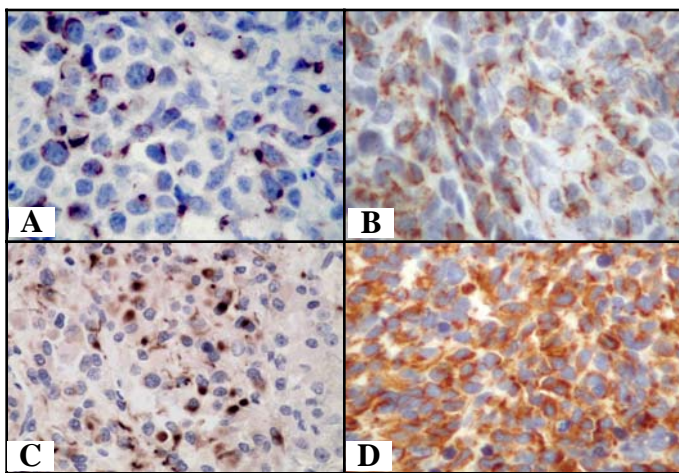
had previously been regarded as metastatic small cell carcinoma. An additional feature of Merkel cell tumor is the presence of perinuclear cytokeratin globs with cytokeratin 20. Cytokeratin 20 is typically absent or only focally expressed in most other high-grade neuroendocrine carcinomas, with the exception of a subset of small cell carcinomas arising in salivary glands. Carcinoid tumor, pancreatic endocrine neoplasms (islet cell tumors), and medullary thyroid carcinoma may also show perinuclear cytokeratin reactivity of variable prominence.

**Renal oncocytoma** is an additional epithelial tumor that shows large perinuclear cytoplasmic globs with low molecular weight cytokeratin antibodies in a subset of cases. The identification of this finding provides strong support for the diagnosis of oncocytomas, as mimics of this tumor commonly encoun-

tered in the kidney do not demonstrate this finding.

**Seminomas** may show dot-like cytokeratin LMW in a subpopulation of cells, and this is reportedly more common in mediastinal tumors (80% of cases) than testicular tumors (20% of cases).

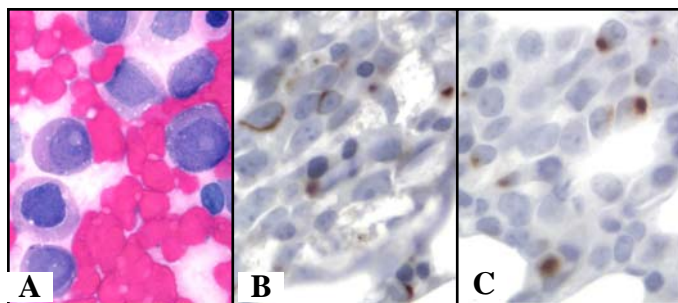
**Granulosa cell tumors** frequently show perinuclear cytokeratin dots, and since these tumors have been known to recur or metastasize many years after the primary is excised, clinicians and pathologists who are faced with metastatic granulosa cell tumors may be unaware of the prior history (a point that I make from personal experience!). The diagnosis of granulosa cell tumor can be confirmed by using additional immunostains, as these tumors are always EMA negative, but typically express inhibin, calretinin, A103, estrogen and progesterone receptors, and smooth muscle actin. **Leydig cell tumor of the testis** may also show perinuclear cytokeratin dots. **Some mesenchymal neoplasms** can show dot-like cytokeratin, including desmoplastic small round cell tumor, monophasic synovial sarcoma, leiomyosarcoma, and rarely gastrointestinal stromal tumors.



A: Cytokeratin LMW stain on mediastinal seminoma. B: Cytokeratin LMW stain on adult granulosa cell tumor of ovary. C: Cytokeratin LMW stain on testicular Leydig cell tumor. D: Cytokeratin 7 stain on desmoplastic small cell tumor.

The most amazing case where I have personally observed cytokeratin dots was a recent case of well-documented **acute myeloid leukemia** (CD45+, myeloperoxidase+, B and T-cell markers neg, etc., etc.). Interestingly, myeloid leukemia cell lines have been shown to express cytokeratin, and there are rare reports of cytokeratin expression in AML patients in the literature (i.e., I found 1 case on PubMed).

In summary, familiarity with the range of tumors that can show this pattern of cytokeratin reactivity provides the pathologist with a list of differential diagnostic possibilities to consider. When taken in conjunction with the clinical setting, morphologic appearance, and other immunophenotypic data, a definitive diagnosis can often be rendered in such cases.



Unusual case of well-documented Acute Myeloid Leukemia in an 82-year-old female presenting with pancytopenia and 40-50% blasts in the marrow. The blasts were peroxidase positive on smears, and CD45, lysozyme, and myeloperoxidase positive in sections. A: Wright-Giemsa stained marrow smear. B: Cytokeratin AE1/AE3 immunostain on marrow core paraffin section. C: Cytokeratin LMW immunostain on marrow core.

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