Fine Needle Aspiration of Renal Masses

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Fine needle aspiration (FNA) biopsy of the kidney is a valuable diagnostic tool primarily reserved for radiographically indeterminate lesions, work-up for metastatic disease to the kidney, and for the diagnosis of inoperable patients. The use of ancillary techniques such as electron microscopy, molecular genetics, and immunohistochemistry enhances the accuracy of the FNA diagnosis.

Renal FNA diagnosis, though accurate, suffers from a high false negative rate. The sensitivity of FNA biopsy of the kidney for malignancy averages about 85% and the specificity averages about 98%. False positive diagnoses are exceedingly rare and are related to sampling adjacent organs, such as the adrenal or the liver. Chronic inflammation, infarction, cysts, hematomas, angiomyolipomas, and other benign lesions may also result in false positive diagnoses.

Cystic Lesions
Most cystic lesions are benign and are either acquired or familial. Solitary cysts are usually acquired and sporadically occur in elderly men, whereas acquired multiple cysts occur in patients who have end stage kidney disease. Foci of renal cell carcinoma can develop in association with a small percentage of these cysts and the majority are either of the clear cell or papillary subtypes. Tumors can have cystic components (eg. cystic nephroma) and tumors can undergo cystic degeneration. Aspirates from benign cysts are usually clear and may contain macrophages. In approximately 20% of the cases, the samples are bloody raising suspicion for malignancy. The smears may exhibit pleomorphic spindle cells admixed with other epithelial cells and contain vacuoles resembling fat. In such cases, differentiating cystic nephroma from renal cell carcinoma or angiomyolipoma can be increasingly difficult based on cytological grounds alone. Other benign cystic lesions of the kidney include polycystic disease which are generally not aspirated. Aspirates from benign cysts are usually clear and may contain macrophages. In approximately 20% of the cases, the samples are bloody raising suspicion for malignancy. Other cystic lesions include polycystic kidney disease which are generally not aspirated.

Solid Lesions
In contrast to cystic lesions, the majority of solid kidney lesions are malignant. In childhood, Wilm’s tumor is the most common renal malignancy and is usually not biopsied. Renal cell carcinoma (RCC), a solid tumor that may undergo cystic degeneration is the most common renal malignancy, accounting for more than 90% of adult cases. Renal tumors are generally solitary, although bilateral tumors are encountered in approximately 2% of patients. The most common type of renal cell carcinoma is the clear cell type (also referred to as conventional).

Clear Cell Carcinoma Subtype
Most common subtype of renal cell carcinoma and is associated with deletion of chromosome 3p, the site of the tumor suppressor gene involved in Von Hippel-Lindau disease. At the time of diagnosis, 25% of the patients have metastasis. Smears are very cellular comprised of large sheets of discohesive vacuolated cells with capillaries traversing through sheets of tumor cells. The tumor cells have abundant vacuolated cytoplasm with indistinct borders, a low N:C ratio and a centrally located round to slightly irregular nucleus with delicate and well-defined nuclear
membranes on both Papanicolaou and Diff Quik stains. The cytoplasm is generally translucent but may be also be granular and eosinophilic in some cases. The grading of the tumor is based on Fuhrman grading of the nuclei. Generally, low-grade tumors have bland nuclear features with delicate chromatin. Higher grade tumors are more likely to have prominent nucleoli, anisonucleosis and nuclear pleomorphism. The sample may be paucicellular if the lesion is sclerotic, or bloody when the lesion is highly vascular.

Differential diagnosis: normal tubular cells, macrophages, inadvertently aspirated hepatocytes, and adrenal tissue. The tumor cells are positive for glycogen and fat and negative for mucin. IHC: positive for cytokeratin, vimentin, EMA and the RCC antigen. These are A103/Melan A and inhibin positive and clear cell RCCA is the opposite with Inhibin and A103/Melan A being negative. In addition, RCC antigen is positive in most RCCA and negative in adrenal neoplasms. Ultrastructural evaluation becomes the arbiter when IHC is equivocal. By EM, clear cell RCCA has the classic combination of intimately admixed lipid and glycogen within the cytoplasm, a rather classic appearance. The adrenal and adrenocortical neoplasms will demonstrate abundant SER, in addition to mitochondria with tubulovesicular cristae and stacks of RER.

**Papillary Renal Cell Carcinoma Subtype**

Accounts for 7-15% of all renal cell carcinomas and is defined by the presence of true papillae in at least 50% of the tumor. Chromosomal abnormalities, such as trisomy of chromosomes 7, 16, and 17, or the loss of the Y chromosome are associated with this tumor. Papillary RCCs are frequently multiple and may be associated with cortical adenomas. Since papillary renal cell carcinoma is usually hypovascular on angiography and may have cystic degeneration, therefore, the tumor is frequently diagnosed by FNA. The tumor has an arborizing arrangement with a fibrovascular core that is better appreciated in cell block sections. The nuclei are bland, sometimes with a groove, and there may be foamy macrophages and psammoma bodies.

IHC: positive for low molecular weight cytokeratin and EMA, RCC antigen and CD10, while negative for CEA and mucin. Differential diagnosis: other papillary neoplasms, such as metastatic disease. The diagnostic pitfalls include differentiating this tumor from high-grade clear cell RCC.

Ultrastructural evaluation shows papillary features with proximal tubule differentiation such as tall microvilli lining tubular structures and abundant mitochondria.

**Renal Cell Carcinoma with sarcomatoid features**

On FNA, sarcomatoid features may be seen in association with other RCC types. Sarcomatoid areas are described in chromophobe (most commonly), clear cell, collecting duct or papillary RCC and this feature is associated with a bad prognosis. FNA of RCC with sarcomatoid features produce cellular aspirates composed primarily of high-grade spindle cells with anisonucleosis, marked nuclear membrane irregularities, and prominent nucleoli; occasional epithelioid cells are also seen. Differential diagnosis: high-grade soft tissue sarcoma and clear cell RCC if the epithelioid component predominates. IHC: positive for cytokeratin and EMA, focally at least, while negative in sarcomas. Vimentin is positive in both sarcomas and in RCC with sarcomatous features and therefore is of no utility. Specific immunomarkers useful for speciating sarcomas such as smooth muscle actin and muscle specific actin for smooth muscle tumors and CD34 for vascular neoplasms such as angiosarcoma and others. Pitfall: poor sampling, since the sarcomatoid spindle cell component may be focal.

EM: RCC with sarcomatous features may have focal epithelial elements such as junctions while sarcomas will have features that pertain to the type of sarcoma having either smooth muscle, striated muscle, fibroblastic differentiation or others.
Collecting Duct Carcinoma
Arising from the collecting duct (distal nephron), this is an aggressive tumor located in the medulla of the kidney, occurring in young individuals and occasionally associated with transitional cell carcinoma of the renal pelvis. Cytogenetic studies may reveal loss of one or more of chromosomes 1, 6, 14, 15, and 21. Medullary carcinoma (a variant of collecting duct carcinoma), occurs in young adults with sickle cell trait or disease and has a worse prognosis. On FNA, collecting duct carcinoma cells have a varied morphology, sometimes resembling a high-grade papillary renal cell carcinoma. The cells are arranged in cohesive groups with the cells having a high nuclear grade with irregular nuclear membranes and scant cytoplasm, which may be vacuolated, suggesting the possibility of metastatic disease. This tumor can have papillae, psammoma bodies and sarcomatoid features on the smears. Differential diagnosis: papillary RCC, high grade urothelial carcinoma and metastatic disease. IHC: positive for high molecular weight cytokeratin, 34BE12, this is in contrast to RCC. Vinculin has recently been proposed as a possible marker for tumors with collecting duct differentiation. Ultrastructurally, these tumors show evidence of distal nephron differentiation with lumina lined by a poorly developed microvillus border.

Chromophobe Renal cell Carcinoma Subtype
Comprises 3-5% of all renal cell carcinomas. Chromosomal abnormalities: loss of chromosomes 1, 2, 6, 10, 13, 17, and 21. Chromophobe RCC can be confused morphologically with oncocytoma especially on cytologic grounds. The smears are cellular, with dis cohesive cells with well-defined cytoplasmic cell borders and a granular eosinophilic cytoplasm. The cells are large and may be pleomorphic with centrally located, round, regular, and sometimes hyperchromatic nuclei. The presence of a perinuclear halo is a clue to the diagnosis. Binucleation, intranuclear inclusions and flocculent cytoplasmic features are some distinguishing characteristics of this tumor. Pitfalls may arise if hepatic tissue or oncocytoma is aspirated. It may be impossible to distinguish oncocytoma from chromophobe carcinoma on cytologic grounds alone. Special stains may aid in differentiating these two tumors; Hale’s colloidal iron is positive in chromophobe RCC while negative in other RCC tumor subtypes. IHC: chromophobe RCC is positive for cytokeratin and negative for vimentin. Ultrastructurally, chromophobe carcinoma has distinguishing characteristics, with numerous mitochondria and aggregates of coalescent round to elongated cytoplasmic vesicles.

Benign Lesions
Oncocytoma
Benign tumors and account for 5% of all renal tumors. Grossly, the tumors are well circumscribed, mahogany-brown on the cut surface, and reveal a central, stellate white scar in the center. Cytogenetic studies: translocation of chromosome 11 and loss of chromosomes 1 and Y. On FNA, uniform, dis cohesive cells with abundant granular cytoplasm and well-demarcated cell borders can be observed. Sometimes, hyaline globules are present within the cytoplasm. The cells have round to oval nuclei with regular contours, with or without inconspicuous nucleoli (low nuclear grade, mostly Fuhrman grade I). The low nuclear grade, the oncocytic nature of the cells and the pushing margin of the tumor grossly are characteristic features that distinguish this tumor from low-grade chromophobe renal cell carcinoma. Differential diagnosis: clear cell RCC and benign hepatocytes that may sometimes be aspirated inadvertently. Pitfalls include differentiating this tumor from other types of RCC. It is important to note that for a tumor with oncocytic cells to be classified as an oncocytoma, the tumor cells must have Fuhrman grade I
nuclei.  IHC: negative for vimentin, usually positive for cytokeratin in contrast to RCC where the cells are positive for both cytokeratin and vimentin. Hale’s colloidal iron stain on the cell block is negative in oncocytoma and strongly positive in chromophobe RCC which helps distinguishing oncocytoma from the eosinophilic variety of chromophobe. EM: easiest way to diagnose oncocytoma since the cells have abundant mitochondria explaining the eosinophilic (oncocytic) appearance of the tumor. Besides, oncocytoma lacks the round vesicles that can be seen in chromophobe carcinomas.

**Angiomyolipoma**

Triphasic benign tumor composed of smooth muscle, mature adipose tissue and variably sized blood vessels. It occurs sporadically in young to middle age women or as familial in young adults with tuberous sclerosis. The majority of the lesions are not biopsied because angiomyolipoma contains fat that can be visualized radiologically. On the contrary, when the tumor fat content is low, aspiration may be warranted. Aspiration poses particular difficulty in interpretation of the smears because of the presence of spindle cells. The presence of predominantly spindle cells may be misidentified as malignant sarcoma. In addition, the presence of epithelioid spindle cells with nuclear pleomorphism and prominent mitotic activity may make it more difficult. The presence of occasional eosinophilic crystals in the spindle cells of angiomyolipoma may aid in differentiating this tumor from others. Another helpful fact is that the spindle cells within the tumor are positive for HMB-45 immunostain. EM: smooth muscle differentiation in a tumor with fat may be a helpful hint. But since this tumor has a characteristic radiologic appearance; it rarely goes for ultrastructural evaluation, except when epithelioid features are prominent and the differential diagnosis is renal cell carcinoma.

**Metanephric Adenoma**

Metanephric adenoma first described in 1995 is a benign tumor that occurs most commonly in women in the fifth decade. It may be associated with polycythemia and the tumor cells are invariably diploid cytogenetically. On FNA, the cells are uniform with round to oval nuclei, inconspicuous nucleoli, and scant cytoplasm. They are arranged in tubules and papillae lined by bland looking cells, forming “glomeruloid bodies”. Psammoma bodies may be observed in the smears. Differential diagnosis: papillary RCC, metastatic lung carcinoma and metastatic papillary thyroid carcinoma. IHC: papillary renal cell carcinomas are positive for EMA while metanephric adenomas are negative. Other useful differentiating markers include TTF-1, CEA and thyroglobulin, which are all negative in metanephric adenoma while CD57 is usually expressed by these neoplasms. Ultrastructurally, the cells of metanephric adenoma have basal lamina and microvilli.

**Metastatic Disease**

Metastasis to the kidney is not uncommon and most of these will have history of a known primary diagnosis. The lung is a common primary tumor site for metastatic disease to the kidney. A diagnosis can be made by histological correlation with the previous biopsy together with the clinical history and the use of ancillary diagnostic techniques. IHC for TTF-1 is positive in many metastases from the lung. Other useful markers are prostatic specific antigen, (PSA) for prostate; leukocyte common antigen, (LCA) for lymphoid and other leukocytic processes, alpha feto protein for liver, RCC antigen for kidney and a combination of cytokeratins, CK7/CK20 to differentiate other organs. The ancillary technique of choice for solving the problem of metastatic disease with an unknown primary is ultrastructural evaluation. Ultrastructurally, there are features, by which tumors can be speciated and the primary site determined.
Other Tumors

Urothelial carcinoma (UC)
UC involves the kidney primarily in the renal pelvis and may be confused radiographically with a RCC large. It accounts for 5-10% of all renal tumors. High-grade tumors usually harbor an aneuploid population of cells. The cytologic appearance depends upon the grade of the tumor. On FNA, low-grade UC have cells typically arranged in sheets and papillae in a clean background. The tumor cells have large hyperchromatic nuclei and moderate amounts of opaque, granular cytoplasm. In high grade UC, the cells are dispersed as isolated cells and occasionally appear in small clusters with a high N:C ratio, scant cytoplasm and hyperchromatic nuclei which may be irregular and have indented nuclear membranes. “Cercariform cells” having long cytoplasmic tails if present in the smears, are very characteristic of high grade UC with squamous differentiation. Pitfall: high grade UC may be difficult to differentiate from a metastatic disease. Immunohistochemistry and molecular studies may be helpful whenever applicable to further characterize the tumor. Typically, UC is positive for keratins 34BE12 and CK20, CEA and mucin.

EM: cells lined with sparse microvilli, joined by junctions, the nature of which depends upon the degree of differentiation of the tumor and have large vesicular nuclei known as telolysosomes.

Lymphoma
Primary lymphoma of the kidney is a controversial and rare disease; however, a handful of cases have been reported in the literature and the majority are diffuse large B cell type. On-site rapid smear interpretation will help in triaging the specimen for flow cytometry and molecular studies. If necessary, an IHC panel may be ordered on the cell block specimen.

Ultrastructurally, lymphomas have very few characteristic features, the lack of which may be helpful especially differentiating them from other tumors that have similar cytologic features such as small cell carcinoma. No intercellular junctions, few organelles which are usually polarized within the cytoplasm of the neoplastic cells.

Conclusion
FNA continues to be the biopsy of choice in the evaluation of renal lesions. FNA biopsy is convenient, has less morbidity, is less expensive, and it is best suited for renal lesions since they are deep seated and difficult to biopsy otherwise. The diagnostic results are comparable to those of a surgical biopsy, especially when combined with ancillary techniques. On-site evaluation of the smear greatly assists in reducing insufficient diagnostic samples. In addition, FNA biopsy of the kidney has proved useful in evaluating incidental renal lesions found during imaging studies for problems unrelated to the kidneys. Overtime, FNA biopsy is a valuable tool, one that has allowed physicians the opportunity to make bold therapeutic decisions while avoiding unnecessary and expensive investigative procedures. The FNA biopsy is also excellent for obtaining material for IHC, molecular studies and EM. Because immunohistochemistry may show increased background, an intrinsic problem with FNA samples, EM can be very useful in addressing diagnostic challenges.

References: