Diagnosis of Tumors of the Kidney: Ultrastructural Classification

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ABSTRACT

Diagnosis of tumors of the kidney depends principally on clinical evaluation and radiologic studies. The role of the pathologist is most important in the classification and characterization of the tumors. In addition, morphologic studies employing the use of electron microscopy may aid in the understanding of histogenesis and the recognition of tumor sub-types. Electron microscopic evaluation indicates specific cellular features characteristic of renal adenocarcinoma, nephroblastoma, and sarcomas. Ultrastructural examination can be particularly useful in distinguishing between sarcomas and sarcomatoid carcinomas and in identifying the origin of metastatic tumors. For these reasons, the use of electron microscopy for the evaluation of renal tumors is recommended in selected cases.

Introduction

Cancer of the kidney is a relatively uncommon form of neoplasia when compared to other sites in the body. Nevertheless, there has been a steady increase in the age-adjusted mortality rate for renal cancer in men. The most recent figures indicate a death rate of 3.7 per 100,000 in the male population, approximately twice the rate in women in whom the mortality rate has remained relatively stable. The reason for the increase in renal cancer in men is unknown.

Diagnosis of tumors of the kidney generally depends on utilization of radiologic techniques. The role of the pathology laboratory in the initial detection of renal tumors has been limited. There are no laboratory tests which specifically indicate the presence of a renal cancer, although some nonspecific methods are available and other potentially useful tests are currently under investigation. Cytologic examination of the urine has been used, but the most successful application of this technique is in the diagnosis of tumors of the lower urinary tract. Urine cytology has proven to be only rarely of value in confirming or excluding the presence of carcinoma of the renal parenchyma. Urinary enzyme assays also do not
appear to contribute significantly to the diagnosis of tumors of the kidney. While the urine levels of lactic dehydrogenase and alkaline phosphatase may be elevated in the presence of renal cancer, they are also found to be elevated in patients with pyelonephritis and other benign conditions.

Nevertheless, the pathologist can make important contributions to the diagnosis and understanding of renal tumors. An area of special interest in recent years has been the ultrastructural classification of renal tumors. While the use of the electron microscope has not been applied to the early detection of such tumors, it has helped to characterize and evaluate the diverse forms of renal neoplasia. The present report reviews the current classification of renal tumors, with emphasis on information derived from ultrastructural studies.

### Major Types of Renal Tumors

The principal categories of tumors involving the renal parenchyma are indicated in table I. The renal adenocarcinoma is the most common, representing between 80 and 90 percent of all kidney tumors. Among children, the nephroblastoma, or Wilms’s tumor, is the most frequent and constitutes about 20 percent of all malignant tumors in children. Mesenchymal tumors, particularly sarcomas, are rarely seen in the kidney but can occur. Transitional cell carcinoma arising in the renal pelvis is excluded from the present analysis. These tumors are generally considered separately from renal parenchymal tumors because of their radiologic presentation as filling defects in the collecting system which clearly distinguishes them from parenchymal tumors and because of their origin from transitional epithelium which relates them more closely to other tumors of urothelial origin arising in the ureter and bladder than to tumors of renal parenchyma.

### Major Types of Malignant Tumors of the Kidney

<table>
<thead>
<tr>
<th>Type</th>
<th>Peak Age</th>
<th>Incidence</th>
<th>Relative Frequency*</th>
<th>Sex Ratio (M:F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal adenocarcinoma</td>
<td>&gt; 40</td>
<td>85.7</td>
<td>2:1</td>
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<td>Sarcomas</td>
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*Data from California Tumor Registry.

### Renal Adenocarcinoma

The origin of the common carcinomas of the kidney from the epithelial cells of the proximal convoluted tubules is now well established. In the past, a variety of terms was used for these tumors such as hypernephroma, clear cell carcinoma, and Grawitz tumor, reflecting the confusion regarding histogenesis. The designation of renal adenocarcinoma is now preferred because it clearly indicates the histologic classification and cell of origin and eliminates the need for a variety of confusing synonyms.

Electron microscopic observations on renal tumors have been critical in resolving the tissue of histogenesis. Ultrastructural studies of renal adenocarcinoma in the rat induced by dimethylnitrosamine and by lead compounds showed the characteristic cellular features seen in the proximal convoluted tubules of the rat. Similar observations have been made in comparing human renal adenocarcinomas with normal proximal convoluted tubules.

Immunologic studies have further strengthened the view that these tumors are derived from cells of the proximal convoluted tubule. Using immunofluorescence methods, it has been shown that antibodies to brush border antigens, which are specific for cells of the proximal convoluted tubule, also react with cells

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**TABLE I**

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from renal adenocarcinoma, while antibodies to Tamm-Horsfall antigen, which is specific for cells of the distal convoluted tubule and loop of Henle, do not. Ultracytochemical studies have provided additional evidence for the similarity of renal adenocarcinoma cells and proximal convoluted tubule lining cells. While the possibility remains that some tumors or portions of tumors may contain antigens of distal convoluted tubule type, current information points to the proximal convoluted tubule cells as the origin for renal adenocarcinomas.

The diagnostic application of the studies on histogenesis or renal carcinomas can be demonstrated by the use of electron microscopy for examining these tumors. Ultrastructural similarities between tumor cells and cells of the proximal convoluted tubule are characteristically found. The features of similarity include a brush border of tightly packed microvilli, pinocytotic vesicles, infoldings of the cell membrane, and abundance of irregularly shaped branching mitochondria.

In addition to these features, the clear cells typically found in renal adenocarcinomas are seen by electron microscopy to contain large amounts of glycogen and lipid material (figure 1). These substances are removed during routine histologic processing imparting a clear appearance to the cytoplasm. In electron microscopic preparations, these organelles are preserved and well demonstrated. It should be noted that the term clear cell carcinoma has been used for a variety of unrelated tumors occurring in various parts of the body.
body. This has led to considerable confusion regarding nomenclature and evaluation of metastatic tumors with unknown or indefinite primary sites of origin. The clear appearance may be a result of intracytoplasmic accumulation of glycogen (clear cell carcinomas of the female genital tract), lipid (lipid cell tumors of the ovary), or both (renal adenocarcinoma). Awareness of the existence of such differences makes the use of electron microscopy particularly helpful in distinguishing metastatic tumors of questionable origin.

The appearance of granular cells seen in some renal adenocarcinomas is accounted for by an accumulation of mitochondria, endoplasmic reticulum, Golgi formations, and lysosomes. Such cells contain relatively little lipid or glycogen. The light microscopic appearance is a result of the density of organelles. The term granular cell tumor has been used for a neoplasm found in a variety of sites, e.g., granular cell tumor of skin, and it is therefore important to be aware that the latter is characterized by dense collections of coarse granules, a feature not seen in cells of renal adenocarcinomas.

In the grading of renal adenocarcinoma, electron microscopy was found to have nothing to add to the light microscopic grading on the basis of nuclear structure. In a series of 22 cases, no ultrastructural characteristic could be found that would have been specific for grading purposes. Similarly, electron microscopy has not been helpful in distinguishing between renal adenomas and adenocarcinomas. The lack of clear histologic distinction between the two has resulted in consid-

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**Figure 2.** Numerous microvilli are evident on surface of cell from renal adenocarcinoma, indicating epithelial nature consistent with tubular origin (× 17,100).
erable controversy regarding the interpretation of small renal cortical tumors of glandular type. Some have suggested that in questionable cases, tumors less than three cm should be considered adenomas. This is clearly an arbitrary separation, particularly since it is known that tumors of small size have been observed on occasion to metastasize. Perhaps the most reasonable approach, in view of the lack of distinguishing features, is to consider all of the tumors adenocarcinomas, with the understanding that small asymptomatic tumors have a generally excellent prognosis but do possess the capacity to metastasize. These observations are consistent with the general experience that the application of ultrastructural analysis in tumor diagnosis is most helpful in tumor classification and identification of specific structures (figure 2) and much less so in grading and distinguishing benign and malignant tumors.

Nephroblastoma

The nephroblastoma, commonly known as Wilms's tumor, is distinctive in its characteristic occurrence in young children and its histologic diversity. The latter feature has resulted in a variety of approaches to the evaluation of histogenesis and classification. The importance of careful evaluation of these tumors has taken on special meaning in recent years because of the successful use of chemotherapy in certain types of tumors and because of evidence that response to treatment may vary in the different sub-types.

Although ultrastructural studies have thus far provided little new insight into the etiology of nephroblastoma, they have

Figure 3. Low magnification electron micrograph of nephroblastoma showing epithelial cells above and mesenchymal-type cells below (× 4600).
brought out special features useful in understanding the histogenesis and classification of the tumors. Several different cell types have been described. These include mesenchymal-type cells, primitive epithelial cells, tubular lining cells, and glomeruloid structures (figure 3).

The mesenchymal-type cells are elongated with large nuclei containing prominent nucleoli and moderate amounts of cytoplasm including free ribosomes, rough endoplasmic reticulum, scattered elongated mitochondria, and Golgi elements. There is evidence of collagen fibril deposition and the cells generally resemble fibroblasts (figure 4). The epithelial cells present demonstrate varying degrees of differentiation. The more primitive cells can be seen by electron microscopy to exhibit close alignment of adjacent cell borders and formation of junctional attachments, including occasional desmosomes. Other epithelial groups show distinct lumen formation with the development of apical junctional complexes characteristic of tubular lining cells and formation of a basal lamina around the groups. Glomerulus-like structures seen by light microscopy are found ultrastructurally to resemble normal appearing glomeruli in some instances. More frequently, the structures show incomplete or aberrant differentiation characterized by lack of one or more of the usual elements present in glomeruli or irregular arrangement of the different cellular elements and basement membrane material.

The ultrastructural findings are generally consistent with epithelial differentia-

Figure 4. Stromal cells of nephroblastoma have characteristics of fibroblasts (× 14,000).
tion toward structures normally formed by the metanephrogenic blastema. The mesenchymal-type elements noted may also be derived from undifferentiated metanephrogenic tissue. It has been suggested that the mesenchymal appearing cells may actually be undifferentiated epithelial cells. Marked similarities in ultrastructure between normal developing metanephron units and epithelial components of Wilms's tumors at varying stages of differentiation have been demonstrated, supporting origin of the tumor from metanephrogenic blastema. Ultrastructural studies of some cases indicating differentiation of cells with Z-bands characteristic of skeletal muscle and cells with neurosecretory-type granules have raised some questions regarding the precise histogenesis of Wilms's tumors. Further electron microscopic studies may help to clarify the origin of these tumors.

**Sarcomas**

Malignant connective tissue tumors of varying types, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, angiosarcoma, and fibrosarcoma, may occur in the kidney. They are quite unusual and the incidence of more than two percent of all malignant tumors of renal parenchyma in the California Tumor Registry collection is probably high based on the referral nature of the case material. Electron microscopic examination of sarcomas of the kidney would be expected to demonstrate the general features of corresponding tumors in soft tissue locations and elsewhere. Ultrastructural studies have been performed on two leiomyosarcomas of the kidney, showing numerous bundles of myofilaments characteristic of these tumors in other sites.

A useful application of electron microscopy is in distinguishing true sarcomas from sarcomatoid carcinomas. The latter are variants of renal adenocarcinoma, as indicated by the presence of junctional complexes, microvilli and intracytoplasmic lumina. These features which indicate epithelial origin and which can be clearly demonstrated by electron microscopy.

The characteristic ultrastructural features of the major types of malignant tumors of the renal parenchyma are summarized in table II.

**Summary**

The main types of malignant tumors of the kidney are generally diagnosed without difficulty by light microscopy. Electron microscopy has been particularly useful in helping to clarify the histogenesis and classification of these tumors. In some instances, ultrastructural study may be important in distinguishing the sarcomatoid variety of renal adenocarcinoma from a true sarcoma and in evaluating tumors with atypical features. Another potentially important application is in the differential diagnosis of metastatic tumors of unknown origin. When presenting in a site other than the kidney, specific identification of an adenocarcinoma of renal origin may not be possible on the basis of light microscopic findings, but distinctive findings seen by electron microscopy may enable definitive diagnosis.
References