Renal Mesenchymal Tumor vs Nephroblastoma: Revisited

John C. Seely

Abstract: Renal Mesenchymal Tumor (RMT) and Nephroblastoma (NB) represent two diagnostically challenging neoplasms of the rat kidney. Both are uncommon tumors reported less frequently than tubule epithelial neoplasms. Excellent guideline criteria exist for both neoplasms. However, in some cases, the diagnosis between RMT and NB may be difficult and occasionally controversial. The most important feature of RMT is the presence of a fibroblastic-like cell which proliferates between tubules and glomeruli. RMT may contain heterogenous tissue such as fibrous, vascular, smooth or striated muscle, cartilage and even bone. On the other hand, NB are usually characterized by the presence of varying patterns of deeply basophilic blastemal cells which are pathognomic for NB. Organoid epithelial differentiation into glomeruloid or epithelial-lined tubules further characterizes NB. The observation of “altered” renal tubule structures in RMT are often a point of confusion with respect to NB diagnosis. In addition, attempts to compare human NB to the rat RMT and NB may be problematic. (J Toxicol Pathol 2004; 17: 131–136)

Key words: rat, kidney, renal mesenchymal tumor, nephroblastoma

Introduction

The diagnostic criteria of Renal Mesenchymal Tumor (RMT) and Nephroblastoma (NB) in the rat have been proposed in several “ guideline” publications representing the cumulative experience and opinion of an international group of knowledgeable pathologists. In most cases, the diagnosis of RMT and NB is straightforward. However, there are some neoplasms which are diagnostically challenging. In this review, the typical features of RMT and NB will be presented along with a brief discussion of the controversial areas between the classification of RMT and NB. Although RMT and NB are both uncommon renal tumors of the rat kidney, continued dialogue among toxicologic pathologists in the refinement of their diagnostic criteria is strongly encouraged.

Induced Neoplasms and Experimental Models

For more than thirty years, the experimental chemical induction of both RMT and NB has been investigated. Experimental models for RMT and NB have included exposure to dimethylnitrosamine and ethylnitrosourea, retrospectively, although a number of additional chemicals are known to induce RMT and NB. The results of many of these studies have already been extensively reviewed. It is apparent from some of the early studies that RMT may have been mis-diagnosed as NB, a point of controversy that still exists today.

Pathologic Features

Spontaneous cases of RMT and NB are uncommon in most rat strains. They occur in both male and female rats and are considered to represent malignant neoplasms, even though they metastasize infrequently. Although NB may be seen in young animals, RMT invariably arise in older animals. The incidence of RMT and NB has been reported to be around 0.10% or less. Some rat strains have a genetically higher incidence of NB and have been used as animal models for the investigation into the development of NB in rats. One strain in particular, the Upj:TUC[SD]spf.nb rat has a high incidence of NB. These rat strains have been useful in determining the early stages of NB and in establishing the hallmark features of NB. RMT tends to arise in the outer medulla or cortex and are infiltrative, irregularly shaped, expansile neoplasms which can become quite large. In some cases, the neoplasm may invade through the renal capsule.

On low power, RMT invariably contain dilated to cystic spaces. Small neoplasms have been noted to be composed of mesenchymal-like tissue (Fig. 3). The putative cell of origin has been reported to be a multipotential spindle-shaped mesenchymal cell based upon the sequential development of RMT induced by dimethylnitrosamine. Evidence of bipotential differentiation was not observed in...
Fig. 1. RMT. (F344-M) Large, expanding neoplasm occupying renal cortex. Several large cysts are present. H&E. ×5.

Fig. 2. RMT. (F344-M) Circumscribed, infiltrative neoplasm consisting mainly of collagenous tissue. Whorling of neoplastic cells around hyperplastic appearing renal tubules. H&E. ×10.

Fig. 3. RMT. (F344-M) Small, mesenchymal-type neoplasm infiltrating around renal tubules and glomeruli. H&E. ×25.

Fig. 4. RMT. (F344-F) Periphery of neoplasm illustrating fibroblastic-like cells infiltrating around renal tubules. H&E. ×50.

Fig. 5. RMT. (F344-M) Dense, fibrosarcomatous area within neoplasm. Tumor cells appear anaplastic with numerous mitotic figures. H&E. ×50.

Fig. 6. RMT. (F344-F) Presence of smooth muscle within neoplasm. H&E. ×50.
these tumors. Characteristic mesenchymal cells may be recognized at the periphery of RMT as fibroblastic-like cells which proliferate between preexisting renal tubules and glomeruli (Fig. 4). One of the most important features of RMT is the whirling of these cells around tubules and glomeruli as they continue to proliferate.

One of the most distinguishing characteristics of RMT is the heterogenous range of connective tissue cell types which may be present, even within a single neoplasm. Areas of fibrous tissue (Fig. 5), smooth muscle (Fig. 6) as well as striated muscle, vascular tissue, cartilage and bone may be observed. In the author’s experience, following a recent review of a large database (NIEHS/NTP) in the F344 rat, most neoplasms consisted of loose to dense fibrous tissue, with occasional smooth muscle to vascular differentiation. The presence of cartilage and/or bone was an uncommon finding. RMT often infiltrate into the renal papilla and invade the renal pelvis. Islands of hyperplastic urothelium may be seen in these cases (Fig. 7).

Profiles of renal tubules which appear hyperplastic are frequently noted in RMT (Fig. 2). These “altered” tubules do not appear to represent a neoplastic component but rather preexisting, entrapped renal tubules. The lining epithelial cells of these tubules appear to be essentially normal and evidence of transition of normal tubules to hyperplastic appearing tubules may be noted. Within some RMT, these tubules are lined by pseudostratified, columnar epithelium with apparent stereocilia and, generally, are regarded as a type of metaplasia (Fig. 8). Fortuitous sections suggest that these tubules may develop from collecting tubules. Some of these “altered” tubules may become quite large and duct-like.

NB have been reported to arise in the renal cortex, preferentially at one of the renal poles. Larger NB may involve most of the kidney and are surrounded by a pseudocapsule of compressed renal parenchyma.

On low power, most NB in the rat are characterized by a triphasic pattern of blastema, epithelial and stromal cells (Figs. 9, 10). The stromal component of most NB is variable and is difficult to determine if it is a neoplastic component of the neoplasm or merely supports the blastema and epithelial...
proliferation (biphasic pattern). The presence of the deeply basophilic blastemal cells is pathognomonic for NB. These cells are characterized by their poorly defined cytoplasm, large nuclei and frequent mitoses. Small foci of immature blastemal cells have been observed in the renal cortex and described as nephroblastomosis or nephrogenic rests. These foci are considered to represent the putative precursor lesions of NB in both rats and humans. Monophasic patterns of NB composed entirely of blastemal cells are infrequently observed generally appearing as undifferentiated and highly malignant neoplasms.

The epithelial component of NB often exhibits organoid differentiation into primitive glomeruli and/or tubules with varying degrees of maturation. In most cases, these epithelial structures are in close approximation to or arise within islands of blastemal cells. Other epithelial structures, within NB, such as profiles of renal urothelium and even some tubules probably represent preexisting epithelium and warrant careful inspection. A rare form of NB is the alveolar type of NB characterized by the presence of small islands of blastemal cells and clear spaces. These aforementioned diagnostic features have been reported from most spontaneous cases of rat NB.

Although monophasic patterns of stromal NB are reported in humans, it is questionable if a similar pattern exists in most rat strains. Mesenchymal rich neoplasms of uncertain origin should have multiple sections examined in order to detect small foci of blastemal cells, thereby, confirming the diagnosis of NB. Muscle, cartilaginous and osseous tissue generally are not seen in rat NB. Several cases of rhabdomyosarcomatous tissue have been reported in the NB genetically predisposed Sprague-Dawley rat, however, it was uncertain if this tissue was neoplastic or metaplastic.
Controversy between RMT and NB

Among renal tumors of the rat kidney, the two most commonly confused neoplasms are RMT and NB\(^3\),\(^4\),\(^5\). This difficulty arises from a number of problem areas including the overall rarity of these tumors, overlapping of similar diagnostic features, the presence of “altered” tubules within RMT and attempts to make direct comparisons of the rat and human NB.

Although comparative aspects of neoplasms are useful in the pathogenesis of lesions and studies involving “tumor models”, not all animal tumors have identical human counterparts. The tendency to compare the rat RMT to human mesenchymal NB does not seem warranted based upon the literature of experimentally induced RMT\(^5\),\(^6\). Human NB tends to differentiate along blastemal/epithelial and mesenchymal cell lines simultaneously and the patterns of some human NB rival teratomas in the diversity and presence of a heterogenous tissue population\(^2\),\(^6\),\(^7\),\(^8\). One human renal neoplasm which seems to be similar to the rat RMT appears to be the congenital or adult form of mesoblastic nephroma, a neoplasm which shares several common features with the rat RMT\(^7\),\(^8\),\(^9\).

Recently, an ongoing project to examine controversial areas of diagnostic criteria between RMT and NB, revealed that the presence of “altered” hyperplastic to metaplastic renal tubules within RMT seemed to be a major point of controversy concerning the tumor diagnosis. Although these structures have been reported to be a feature of RMT, the photographic spectrum of these tubule changes has not been adequately represented in the literature. As previously described, tubule changes may be significant within some RMT and occasionally noted in NB and lipomatous tumors of the rat kidney\(^3\),\(^4\),\(^5\). Although the mechanism for these tubule changes are not known, the unique relationship during renal development between the primitive metanephric mesenchyme and epithelial tubules derived from the ureteric bud (Wolffian duct origin) might suggest that these tubules are recapitulating embryonic histogenesis. Furthermore, it is possible that the presence of expressed molecules or “tumor factors” may be a stimulatory component of this response. A number of transcription factors, signaling molecules or growth factors have been shown to influence the reciprocal mesenchymal-epithelial interaction of the developing kidney\(^3\),\(^6\),\(^8\).

Summary

Current dogma differentiates the rat RMT and NB into two distinct tumor types. The histogenesis of the rat RMT appears to be uniquely different from the rat or human NB. It is clear that further studies are needed to clarify a number of issues regarding our understanding of the rat RMT and NB. Newer immunohistochemical staining and molecular probes should be applied to these neoplasms in an attempt to answer some of these issues and resolve ongoing areas of controversy.

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References


