History of Renal Neoplasia

Brett Delahunt MD FRCPA FRCPath

Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago - Wellington, Wellington, New Zealand

Early Observations

The earliest reference suggestive of tumor arising in the kidney was made by Daniel Sennert in his text *Practicae Medicinae*, first published in 1613. In this Sennert states; “Moreover the hard swelling of bad kidneys which has the capacity to throw a person into cachexia and dropsy, is for the greater part incurable”.

Rayer in the introduction to his series of renal tumors published in 1841, discussed the significance of these observations and suggested that Sennert’s comments referred to sclerosing chronic inflammation of the kidney rather than malignancy. Rayer also reviewed two earlier reports, previously considered by Chopart (1791) to be renal carcinoma. The first case, described by Seger in 1673, was a renal tumor that appeared to be an abscess complicating nephrolithiasis. The other case, published by Thomas Bonet in 1679, noted that the kidney was turned into a sort of pocket; the patient experienced intermittent hematuria, and the likely diagnosis was carcinoma of the renal pelvis.

The earliest unequivocal case of renal carcinoma was published by Miril in 1810. He described the case of Françoise Levelly, a 35 year old woman, who presented to Brest Civic Hospital on April 6, 1809, supposedly in the late stages of pregnancy.

The first classification of renal tumors based on a macroscopic morphology was published by Koenig in 1826, who divided the tumors into scirrhous, steatomatous, fungoid and medullary forms. In his series of thirteen cases, Rayer classified renal tumors into three groups based on clinical and gross pathological findings.

In 1842, Cruveilhier published his *Atlas of Anatomical Pathology*, which included a case of renal carcinoma antedating those illustrated by Rayer in his Treatise and Atlas of 1837-1841. The patient was a 53 year old woman who had been admitted to the Maison Royale de Santé on June 9, 1828, in a debilitated and emaciated state.

Following publication of Rayer’s series, other authors examined the tissue of origin for renal carcinoma. Robin thought that the tumor was derived from renal tubular epithelium. Kupffer suggested in 1865 that renal tumors were not of renal tubular origin but resulted from malignant change of intrarenal Wolffian rests. Waldeyer thought that the tumor was derived from renal tubular epithelium, an observation accepted by Klebs in 1876 and Lancereaux in 1889.

The Hypernephroma Controversy

The pathogenesis of renal epithelial tumors has provided one of the most enduring controversies of modern surgical pathology. The debate was initiated by Paul Grawitz when in 1883, he published his observations on the morphology of small, yellow predominantly subcapsular renal tumors that had previously been described as lipoma. Grawitz compared
these small tumors to the normal adrenal gland and cortical hyperplasia of the adrenal, and concluded that they represented small ectopic adrenal rests (struma suprarenalis aberrata). He postulated that these adrenal rests were the source of small subcapsular renal cortical tumors that were not usually malignant in character.

Grawitz’s theory stimulated considerable interest and was widely accepted, in part because of its concurrence with Cohnheim’s cell rest theory. Chiari, in 1884, gave his support to the concept in a case report of a 44 year old man with a large pelvic tumor of probable renal origin that recurred following surgical removal.

Grawitz consolidated his theory in 1884 with further illustrations of intrarenal ectopic adrenal tissue, and concluded that only alveolar tumors were of adrenal origin, whereas papillary tumors were derived from renal tissue. Grawitz consolidated his theory in 1884 with further illustrations of intrarenal ectopic adrenal tissue, and concluded that only alveolar tumors were of adrenal origin, whereas papillary tumors were derived from renal tissue.

The first serious challenge to Grawitz arose in 1893 when Sudeck published descriptions of renal tumors in which he identified atypical features within renal tubules and noted a gradation in atypicality between these tubules and neighboring malignant tumor. The publication of Sudeck’s paper stimulated further interest, although the majority of subsequent reports favored Grawitz’s concept. Lubarsch in 1894 supported the adrenal rest theory by coining the term hypernephroid tumor, later amended by Birch-Hirschfeld to hypernephroma, to describe these tumors.

Reports published in the following 14 years continued the debate, with the majority of authors preferring an adrenal gland or adrenal rest origin for these tumors, although there were occasional dissenting reports, such as that of Kelynack, who believed the tumors to be of renal epithelial origin.

Vigorous criticism of Grawitz was provided by Stoerk in 1908, who considered the adrenal origin of renal tumors to be unproved. He compared the relative frequency of renal tumors with the scarcity of malignant epithelial tumors of the adrenal gland and commented on the lack of histological similarity between hypernephroma and adrenal carcinoma.

Despite these compelling arguments, the term hypernephroma, with its associated adrenal connotation, persisted in the literature.

Newcomb, after a careful study of 5,201 autopsies, suggested a renal origin for Grawitz tumors, as did Karsner, who proposed the terms renal carcinoma and malignant nephroma to describe these malignancies.

Foot and Humphreys, and Foote et al. introduced the term renal celled carcinoma to emphasize a renal tubular origin for these tumors. Their designation was slightly altered by Fetter in the discussion section of the latter report to the now widely accepted renal cell carcinoma.

Convincing evidence to settle the debate was offered by Oberling et al. in 1959 who studied the ultrastructure of clear cells from eight renal carcinomas. They found that the tumor cell cytoplasm contained numerous mitochondria and deposits of glycogen and fat. They identified cytoplasmic membranes inserted perpendicularly onto basement membrane with occasional cells containing microvilli along the free borders. They concluded that these features indicated that the tumors arose from the epithelial cells of the (renal) convoluted tubule, thus finally settling one of the most debated issues in tumor pathology.
Renal Adenoma

The term renal adenoma has been included in most classifications of neoplasms of the renal tubules, but its definition and relationship to renal cell carcinoma has been controversial.

The designation “renal adenoma”, referring to benign tumors of the renal parenchyma, was first used in the classifications proposed by Sturm in 1875 and by Klebs in 1880. Sturm distinguished between solitary and multiple adenomas of the kidney, and postulated that in time, “benign” adenomas could show transformation into carcinomas. Renal adenomas were subsequently classified into papillary and alveolar types by Weichselbaum and Greenish, whereas Sabourin described two forms of multiple renal adenomas that were differentiated by the presence of cuboidal or cylindrical cells. In these early reports, the authors distinguished between adenomas and their malignant counterpart on the basis of tumor size and circumscription, and the absence of metastases.

Burkhardt considered adenomas to have a malignant potential being the precursor lesions of malignant tumors of the renal parenchyma, whereas Green and Brooks were unable to differentiate between adenomas and hypernephromas on histological grounds and considered that most of the tumors previously described as adenomas should be reclassified as hypernephromas. A continuum between benign renal adenomas and carcinomas was also postulated by Stoerk in 1908, Gerlach and Gerlach in 1915 and Arkin in 1926.

The frequency of occurrence of renal adenomas varied considerably in early reported series. Prior to 1883 renal adenomas were considered to be rare; however, Grawitz reported finding three examples in routine post-mortems over a 5 week period. A year earlier, Weichselbaum and Greenish found adenomas in 10% of postmortem subjects over 70 years of the age, whereas Zehbe collected 250 cases of which 40% were solid and 60% had a papillary or alveolar pattern. Hefke found 45 papillary and 8 alveolar adenomas in addition to 8 adrenal rests in 500 consecutive autopsies.

In 1938 Bell reclassified renal tumors, basing his observations on the results of 30,000 autopsies. He grouped adenomas and adenocarcinomas into one group and differentiated between these and multiple adenomas associated with atherosclerotic kidneys, for which he claimed there was no clinical evidence of malignant potential. Bell was unable to distinguish histologically between benign and malignant forms in his adenoma-carcinoma group. He divided the tumors according to size and noted that only one tumor <3cm in diameter had metastasized. He concluded his classification with the statement that “although the size of the tumor is not a certain criterion as to malignancy … we may say that tumors not over 3cm in diameter have rarely formed metastases”. In his enlarged series, 65 tumors <3cm in diameter were found to have undergone metastatic spread. Despite these conflicting results, Bell arbitrarily classified all solid tumors <3cm in diameter as adenomas but qualified this by stating that all solid adenomas appeared to be small carcinomas.

The concept that tumors <3cm were adenomas was widely embraced and was not formally dispelled until publication of the Heidelberg/Rochester Classification in 1997.

Classification of Renal Tumors

The resolution of the question regarding the tissue of origin of renal cell carcinoma gave rise to a rational bias for the classification of renal epithelial neoplasia. In many of the early classifications malignant tumors were grouped together regardless of their histologic architecture. As late as 1981, the first edition of the WHO classification simply divided
carcinomas of the renal parenchyma into \textit{renal cell carcinoma} and others.\cite{27} Despite this failure to acknowledge the existence of different morphotypes of renal neoplasia by the WHO in 1981, important advances in our understanding of the diversity of these tumors were being made. In 1976 the first series of papillary renal cell carcinoma was reported\cite{28} and in the same year a series of 13 cases of renal oncocytoma was published.\cite{29} In 1985 Thoenes’ group described chromophobe renal carcinoma\cite{30} and a year later this was incorporated into the Mainz Classification,\cite{31} which was based upon the morphology and the putative tissue of origin of each tumor group. The recommendations of Mainz Classification were reinforced by studies that showed each of the tumor morphotypes to have differing cytogenetics, and with minor modifications were endorsed by the Heidelberg (1996) and Rochester (1997) Consensus Classifications.\cite{32,33} An important feature of both of these consensus classifications was the acknowledgement that diagnostic criteria should be rigidly adhered to and if tumors exhibit atypical features these should be classified as \textit{renal cell carcinoma unclassified}.\cite{4} The application of this recommendation has led to the identification of several novel forms of renal cell neoplasia, with mucinous tubular and spindle cell carcinomas\cite{34} and translocation carcinomas,\cite{35} being added to the 2004 edition of the WHO classification of renal tumors.\cite{36} Since then other novel morphotypes of renal carcinoma have been described and it is anticipated that these will be recognized in the next edition of the WHO classification.

\textbf{References}

12. Kelynack TN. Renal Growths, 1898. Their Pathology, Diagnosis and Treatment. YJ Pentland, Edinburgh.