Renal neoplasias developing in ends stage kidney disease secondary to therapeutic modalities

PhD thesis

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ABBREVIATION LIST

ESRD: end stage renal disease

RCC: renal cell carcinoma

EMA: epithelial membrane antigen

HMWCK: high molecular weight cytokeratin

KSC: kidney specific cadherin

CaOx: Calcium oxalate

CaOx +: Calcium oxalate pozitive

CaOx -: Calcium oxalate negative

PAS: Periodic Acid-Shiff

ACKD: Aquired Cystic Kidney Disease

SUMMARY OF NEW RESULTS:

1. The Ph.D theses discusses renal cell carcinomas developing in the acquired cystic kidney disaes secondary to dialysis treatment.
2. The Ph.D theses describes a new phenotypic variant of renal cell carcinoma (called oxalate type by the authors) associated with intratumoral Calcium Oxalate depositon. The study suggests the need for a new classification system.
3. Immunohistochemical characterizationi of the new „oxalate type" renal cell carcinoma.
4. Discussion of role of the new renal cell carcinoma phenotype and its differentiation in the CaOx deposition .
5. The first case description of a carcinoasarcoma developed in a transplant kidney.

INTRODUCTION:

For patients suffering from end stage renal disease the only therapeutic option is dialysis until a kidney becomes available for transplantation. The prevalence of neoplastic disease affecting the urinary tract in both the dialysed and the transplantated patient population is increased.

Acquired cystic kidney disease (ACKD) is characterized by small cysts randomly distributed throughout the renal cortex and medulla of patients with end-stage renal disease (ESRD) unrelated to polycystic kidney disease (Dunnill, et al., 1977; Grantham, 1991; Ishikawa, 1991; Ishikawa, et al., 1990; Matson and Cohen, 1990; Truong, et al., 1995). Both the prevalence and severity of ACKD increase with the duration of ESRD and ACKD has been reported in almost all patients after more than 10 years of dialysis (Ishikawa, 1991; Matson and Cohen, 1990).

Renal neoplasm is noted in 4.2-5.8% of ESRD patients, reflecting a marked increase in its incidence compared with the general population(Hughson, et al., 1986; Ishikawa, et al., 1990; Matson and Cohen, 1990; Truong, et al., 1995). Although these neoplasms were rarely reported in a shrunken kidney without cystic changes, the vast majority of them develop from the background of ACKD(Hughson, et al., 1980; Ishikawa, et al., 1990; Truong, et al., 1995). The involvement is usually bilateral/multifocal and displays a spectrum of closely associated lesions including simple cysts, cyst lined by hyperplastic epithelium with or without atypia, adenoma, and renal cell carcinoma (RCC) with or without metastasis(Dunnill, et al., 1977; Hughson, et al., 1986). Some previous studies have suggested that the histologic types of RCCs in this context are similar to those in the general population but with overrepresentation of the papillary RCC (Dunnill, et al., 1977; Hughson, et al., 1996; Ishikawa and Kovacs, 1993; Truong, et al., 1995). In fact, the histologic features of ACKD-associated RCCs are not well studied and

many of these tumors do not fit in any categories in the current classification of renal neoplasms(Denton, et al., 2002; Tickoo, et al., 2003). One of the distinctive features of ACKD-associated RCCs is intratumoral deposition of calcium oxalate (CaOx), which was previously reported in four cases and briefly mentioned in a recent abstract(Denton, et al., 2002; Tickoo, et al., 2003). This feature, to the best of our knowledge, has not been described in RCCs in the general population. Although this finding seems unique for ACKD-associated renal neoplasms, many pertinent features including its frequency, pathogenesis and biologic implications, and the histologic type of the involved RCCs are not known.

For patient suffering from end stage renal disease the transplantation is the ulimate therapeutic solution. As a result of the increasing number of tranplant centers and the use of immunosuppressive therapy, the patients' life expectancy is markedly increased and the quality of life dramatically improved. Besides the infection and graft versus host disease secondary to the immunosuppressive treatment the increased incidence of neoplastic diseases in post-transplant patients is a major concern. Geographic difference can be observed in the prevalence of malignancies (USA: 6%, Europe: 1-9%. Australia: 18,3%). After kidney transplantation Kaposi's sarcoma, non-Hodgkin's lymphomas, and non-melanoma skin cancers represents the most common secondary neoplasms (more than 20-fold increased than in the general population), the increase of genito-urinary (G-U)malignancies is also substantial (15-fold increase) (Kasiske, et al., 2004; Samhan, et al., 2005). The incidence of G-U tumors varies between 0.64-1.67%. Since the incidence, type and other characteristics of prost-transplant malignancies varies in different geopraphic regions, many mechanism can play role in the etiology such as: (1) defect in immune survailance mechanism, (2) incresed sensitivity for oncogenic virus infection, (3) lymphoproliferation affecting immunologic feed back mechanism, (4) uremia as a predisposing condition. There are three distinct type of post-transplant renal neoplasms. The

tumor can develop in the (a.) donor's or (b.) recipient's kidney prior the transplantation, which emphasises the importance of pretransplant renal ultrasonograph examination and cystoscopy. The third group is the de novo malignancies, which can develop in the patient's own (90%)or in the tranplanted kidney (10%) (Penn, 1998). The prevalence of de novo renal cell carcinomas is higher (4.1-4.6%), than of the sporadic cases. It is important to mention the unusually high percentage of renal pelvis tumors (15%) among de novo carcinomas (Penn, 1998).

In my studies I characterized the morphological appearance and immunological expression profile of the renal neoplasias developing in ends stage kidney disease secondary to therapeutic modalities with special attention to those neoplasms with calcium oxalate deposition . Beside reviewing the literature I also first describe a rare type of neoplasm presented in a transplanted kidney.

MATERIALS AND METHODS:

I. Neoplasms developing in the native kidneys of the dialysis treated patients

The study features 30 end-stage renal disease (ESRD)-associated RCCs identified within a 13-year period, including eight with CaOx deposition, were analyzed. Pathologic and clinical features of CaOx positive (+) and negative (-) RCCs were evaluated and compared.

II. Neoplasm developing in renal transplant patients

The study describes a renal carcinoasarcoma developed in an allograft kidney and reviews neoplastic diseases arising in transplant patients with special attention to genito-urinary neoplasms.

RESULTS:

I. Neoplasms developing in the native kidneys of the dialysis treated patients

The CaOx+ RCCs showed higher tendency for bilaterality and multifocality. Seven tumors displayed distinctive morphologic features characterized by tumor cells with ill-defined cell membrane, abundant granular eosinophilic cytoplasm, large nuclei, and prominent nucleoli. One tumor was of clear cell type. Regardless of histologic type, all tumors displayed a proximal tubular differentiation. No significant difference was noted for tumors' stage, proliferation and apoptosis rate between the CaOx+ and CaOx- RCCs.

II. Neoplasm developing in renal transplant patients

A multifocal urothelial carcinosarcoma of a transplanted kidney in a 49-year-old woman is described. The performed immunohistochemical characterization revealed the CK positivity of both the epithelial and the sarcomatoid areas. Vimentin expression of the sarcomatoid component was also noted. Genomic analysis of the extracted nuclei of all the neoplastic cells showed uniformly XY genotype proving the transplant origin of the tumor. The occurence of the carcinosarcoma is extremly rare, our case represents the first published case in the english literature.

DISCUSSION:

I. Neoplasms developing in the native kidneys of the dialysis treated patients

This comprehensive evaluation of CaOx+ RCCs in ESRD patients shows that they are not rare and indeed accounted for 8/30 (27%) of all RCCs developing from this background. This high incidence is somewhat surprising because only 19 CaOx + RCCs were previously reported (Dry and Renshaw, 1998; Rioux-Leclercq and Epstein, 2003) and this type of RCC was not mentioned in any large studies on ESRD-associated renal neoplasms (Denton, et al., 2002; Doublet, et al., 1997; Dunnill, et al., 1977; Hughson, et al., 1986; Hughson, et al., 1980; Hughson, et al., 1996; Ikeda, et al., 2002; Ishikawa, et al., 1990; MacDougall, et al., 1987; Miller, et al., 1989; Takebayashi, et al., 2000; Truong, et al., 1995). Since CaOx crystals are colorless but highly visible under polarized light in the hematoxylin-eosin stain and were dissolved during the periodic acid-Schiff or Mason's trichrome stains, which are frequently used to evaluate ESRD-associated renal parenchyma changes, they may be overlooked unless the deposition is extensive or polarized light is routinely used. Although the high incidence in our study may be related to the fact that CaOx was specifically sought for in all RCCs, extensive deposition involving more than 75% of tumor areas were noted in 4/8 (50%) of these tumors. A recent abstract documented that 15 out of 43 (35%) RCCs in ESRD patients contain CaOx, supporting our observation that these tumors are not rare (Tickoo, et al., 2003).

Our study together with previous reports (Dry and Renshaw, 1998; Rioux-Leclercq and Epstein, 2003; Tickoo, et al., 2003) indicates that intra-tumoral CaOx deposition is a unique features of ESRD-associated renal neoplasms including RCCs, since, to the best of our knowledge, it has never been described in renal neoplasms in the general

population and, indeed, was not observed in any of the 346 RCCs unrelated to ESRD during the studied period. Previous studies by Dry *et al*, Rioux-Leclerq *et al*, and Tickoo *et al* suggested that intra-tumoral CaOx deposition is associated with a distinctive morphologic profile (Dry and Renshaw, 1998; Rioux-Leclercq and Epstein, 2003; Tickoo, et al., 2003). The current study confirms and expands this observation, i.e., this profile is observed in almost all RCCs with CaOx deposition but only rarely seen in RCCs without it. Furthermore, this profile does not fit neatly into the current histological classification of renal tumors (Storkel, et al., 1997).

Almost all CaOx+ RCCs were composed entirely or almost entirely of tumor cells with cuboidal abundant eosinophilic granular cytoplasm, focal but prominent cytoplasmic vacuolization, ill defined cell membrane, and a Furhman's nuclear grade 3. These tumors, however, have diverse growth patterns including predominantly papillary, tubulopapillary, or solid/cribriform types. Although the amount of intra-tumoral CaOx is variable, the deposition is extensive and accounts for more than 75% of tumor areas in at least 50% of our cases. Indeed, tumor calcification was obvious on imaging studies of two of these cases. The CaOx deposition was not associated with any distinctive tissue reaction such as necrosis, fibrosis or inflammation only one case showed multinucleated giant cell reaction. This morphologic profile correlates well with intra-tumoral CaOx since it is noted in seven out of eight CaOx+ RCCs in the current study, all five previously reported CaOx+ RCCs, and all 15 CaOx+ RCCs in a recent abstract that included 43 ESRD-associated RCCs (Dry and Renshaw, 1998; Rioux-Leclercq and Epstein, 2003; Tickoo, et al., 2003). On the other hand, this morphologic profile was found in only 1/18 CaOx- RCCs in the current study and none of the 28 CaOx- RCCs in another study (Dry and Renshaw, 1998; Rioux-Leclercq and Epstein, 2003; Tickoo, et al., 2003). This phenotype, however, is not pathognomic for intra-tumoral CaOx, since one RCC

with extensive CaOx deposition in our study displays typical clear cell features.

The biologic significance of CaOx+ RCC as a distinctive subset of ESRD-associated RCC is not clear. Although bilaterality and multifocality is well known for ESRD-associated RCCs (Ishikawa, et al., 1990; Matson and Cohen, 1990; Truong, et al., 1995), we found that these features are significantly more frequent for the CaOx+ RCCs than for its CaOx- counterpart (40 *vs.* 0% for bilaterality and 57 *vs* 11% for multifocality in the current study. This observation suggests that CaOx deposition, which is known to be quite frequent and often extensive in kidneys with ESRD, may promote tumor development or, alternatively, the genetic changes that predispose to CaOx deposition also promote malignant transformation.

The durations from dialysis to RCCs in our cases were 8-11 years (mean 9.2 years). This is significantly longer than the mean duration of 5 year reported by Houghson *et al* for ACKD-associated RCCs (Hughson, et al., 1986; Hughson, et al., 1980; Hughson, et al., 1996), regardless of histologic subtype. This difference suggests that the increased bilaterality and multifocality of CaOx+ RCCs may be at least in part related to the duration of dialysis. On the other hand, we have noted that CaOx deposition was always significantly more in CaOx+ RCCs than in the adjacent kidney tissue but the renal tissue deposition of CaOx was not different between those with CaOx+ RCCs and those with CaOx- RCC. These observations suggest that CaOx deposition within the tumor itself may be related to their behavior. Although the majority of ESRD-associated RCCs develop from the background of ACKD, those without associated ACKD have been noted and they account for 9-25% of all ESRD-associated RCCs (Denton, et al., 2002; Tickoo, et al., 2003). In contrast, all CaOx+ RCCs (eight in the current study, five previously reported, and 15 in a recent abstract) are associated with ACKD (Dry and Renshaw, 1998; Rioux-Leclercq and Epstein, 2003; Tickoo, et al., 2003). These observations suggest some

pathogenetic links among tumor bilaterality/ multifocality, renal cyst formation, renal parenchymal CaOx deposition, and intra-tumoral CaOx deposition. Regardless of the pathogenetic implication, our findings imply that the diagnosis of CaOx+ RCC should entail appropriate clinical follow-up for progressive renal cystic change and renal tumors of the contralateral kidneys.

Why CaOx is deposited in only some ESRD-associated RCCs, but not RCC in general, is not clear. Our study suggests at least two responsible factors, i.e., increased serum level of oxalate and a specific cell phenotype that can promote oxalate deposition. Since kidney is the only organ through which oxalate is eliminated, increased serum level of oxalate is expected along with chronic renal failure regardless of etiology (Salyer and Keren, 1973). It is estimated that serum oxalate level starts to increase when glomerular filtration rate is less than 25ml/ minute (Morgan, et al., 1987) . Since dialysis can only remove a fraction of the daily oxalate intake, this positive balance is even worse in ESRD patients and the serum level as well as the body burden of oxalate in these patients is progressively increased (Hoppe, et al., 1999; Worcester, et al., 1994). In physiologic condition, oxalate is freely filtered through the glomerular capillaries and undergoes bi-directional transport through the proximal tubules resulting in increased concentration in the tubular lumen, whereas other portions of the nephron do not participate in handling of oxalate (Hatch and Freel, 2003) . Our study indicates that the immunoprofile of the CaOx+ RCCs is quite uniform with pronounced expression of markers for proximal tubular differentiation including the RCC marker and CD10 and absent or weak expression of the markers for distal portion of the nephron such as KSP, HMWCK, or EMA. These observations suggest that proximal tubular differentiation may play a crucial role in promoting intra-tumoral CaOx deposition. We also propose that it is the proximal differentiation, rather than light microscopic phenotype, that is important for CaOx deposition since the

only CaOx+ clear cell RCC known to us also displayed strong proximal differentiation, like those with the "oxalate" phenotype. In contrast, all CaOx- RCCs in our study showed predominantly distal nephron differentiation, even though several of them are of clear cell or papillary types, which are known to derive from proximal tubules in the sporadic RCC (Kim and Kim, 2002; McGregor, et al., 2001). Our study also demonstrated that CaOx may deposit in adenomas, cysts, or dilated tubules, but only in those with an immunoprofile of proximal tubular differentiation, further implicating its role in renal CaOx deposition. Additional factors may be involved in CaOx deposition. Several molecules are known to inhibit CaOx crystal formation in physiologic condition, including nerphrocalcin, osteonectin, mannan-binding lectin associated plasma protein, and FK506-binding protein, some of which are immunolocalized to renal proximal tubules (Ikeda, et al., 2002). It is possible that lower levels of these molecules may promote CaOx deposition. Although this hypothesis has not been tested, at least one of these molecules, i.e., nephrocalcin was identified in RCCs and shown to decrease in ESRD-associated RCCs (Michaels, et al., 1998). Whether this decrease is limited to the CaOx+ tumors in this context is not known.

CaOx is known to induce significant changes in cultured tubular cells. It may be mitogenic at lower concentration but may cause cell necrosis or apoptosis at higher concentration (Koul, et al., 1994; Scheid, et al., 1996) . CaOx can induce intracellular formation of reactive oxygen species and inhibit several cytosolic enzymes, which may account for its cytotoxic effects (Koul, et al., 1994; Scheid, et al., 1996). CaOx is the major factor in renal tissue injury in renal oxalosis, a condition characterized by renal tissue deposition of CaOx. In the context of ESRD, CaOx was thought to promote cyst and tumor formation through both mechanical obstructions of renal tubules and regulation of tubular cell cycles révén (Hughson, et al., 1986; Ishikawa, 1991; Lieske, et al., 1992; Truong, et al., 1995). What impact

that intra-tumoral CaOx has on tumor cells, however, is not clear. In the current study, we did not observe in the majority of cases (7/8) any specific tissue reaction in the tumor tissue around the CaOx crystals, only one case showed multinucleated giant cell reaction. Furthermore, the rates of tumor cell proliferation and apoptosis of the CaOx+ RCCs as determined by Ki 67, a specific cell proliferation marker, and *in situ* end-labeling of fragmented DNA, respectively, were widely variable among CaOx+ RCCs but were not significantly different from those of CaOx- RCCs. These features suggest that CaOx deposition may not have any significant impact on tumor cell kinetics.

The behavior of ESRD-associated RCCs, especially those develop in the context of ACKD, is well known. Compared to sporadic RCCs, these tumors are usually of lower grades, lower stages, with a lower metastatic rate and a better survival (Truong, et al., 1995). However, the behavior of different histologic subtypes of RCCs, including the CaOx+ ones, within the broad category of ESRD-associated RCC is not known. Although the CaOx+ RCCs displayed a higher nuclear grade than the CaOx- RCCs, this study suggests that in the context of ESRD, they have the same behavior since no significant difference was noted in these two groups for the tumors' stage, proliferation rate, and apoptotic rate, and the patients' survival. Nevertheless, this suggestion needs to be corroborated in further studies with more cases

II. Neoplasm developing in renal transplant patients

The transplantation provides a better quality of life for the patients if compared to dialysis. The risk of neoplastic diseases is increased after transplantation due to the immunosuppressive therapy. This increased risk, though it is still present, is less prominent if we compare it to the dialysis treated patients.

After transplantaton the majority of renal neoplastic proliferations develop in the native kidney, a small proportion

of post-transplant malignancies can also arise in the donor organs. The majority of these neoplasms are renal cell carcinoma , but the relative proportion urothelial carcinoma of the renal pelvis is increased (15%) (Penn, 1995)compared to the sporadic cases (8-10 %). Of course, most of these tumors are urothelial carcinoma, but previously in transplanted kidney not reported rare types of cancer can occur in this location.

SUMMARY

Renal neoplasm is noted in 4.2-5.8% of ESRD patients, reflecting a marked increase in its incidence compared with the general population. In summary, CaOx+ RCCs accounts for a significant portion of all ESRD-associated RCCs. Almost all of these RCCs display a distinctive morphologic profile, which does not fit the current histologic classification of RCC. These RCCs seems to have the same relatively good prognosis shared by other ESRD-associated RCCs

The transplantation provides a better quality of life for the patients if compared to dialysis. The risk of neoplastic diseases is increased after transplantation due to the immunosuppressive therapy.

Both dialyzed and transplanted patients should be monitored for the development of malignancy in native kidneys, the allograft and elsewhere.

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impact factor: 1.395

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impact factor: 2.938

Összesített impact factor: 35.795

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