

Acquired Cystic Kidney Disease

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1977 Mike Dunnill from Oxford first identified the presence of renal tumors in a new form of cystic kidney disease occurring in pts on long term intermittent hemodialysis.

Systemic autopsy study of 30 HD patients.

- 14 had extensive renal cysts
- 6 of them had renal carcinomas
- 1 with metastatic disease.



Diagnostic Criteria

Acquired cystic kidney disease
Minimum of 3 cysts

Renal failure

No cysts before onset of renal failure

No family history or clinical features of other renal cystic disease

Kidney usually small or normal size

Extensive chronic renal damage



Incidence

Matson 1990: In 130 pts with advanced CKD or ESRD
7% ACKD in CKD and 22% in dialysis pts.

Duration of dialysis: 28 months in those with 1-3cysts, 49 months in those with ACKD.

50-80% of pts may be affected after >10yrs of dialysis.

Kojima 2006: In 2624 dialysis patients 81.8% had ACKD on a median dialysis time of 11yrs. 44pts (1.68%) showed evidence of renal carcinoma.



Features of ACKD

Multiple and bilateral cysts

Usually less than 0.5cm but can be as large as 2-3cm

Cysts are located only in the kidney

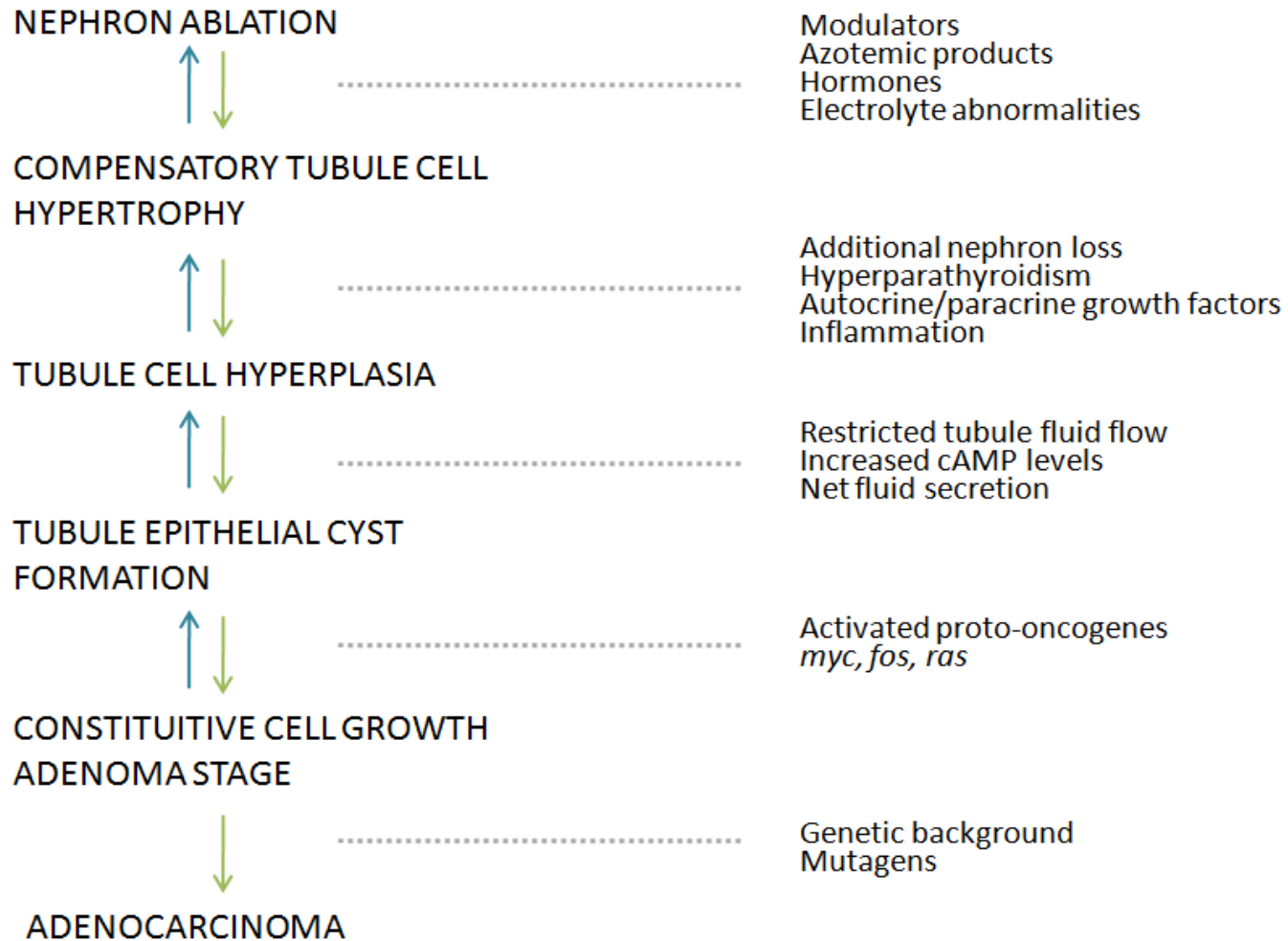
Can begin prior to dialysis

(occurrence in pts with CrCl as high as 70ml/min, however majority in pts w/ CrCl 50ml/min)

Men and blacks are at much higher risk



Pathogenesis



Grantham 1991

Azotemic / Chemical Influence

In rats with normal kidneys **diphenylamine, diphenylthiazole, or nordihydroguaiacetic acid** causes damage of renal epithelium and leads to focal tubule dilatation and expansion. (Welling 1985)

Cyst formation can be reversed by stopping chemical exposure.

The cyst formation from nordihydroguaiacetic acid is significantly enhanced by exposure of the animals to **endotoxins** or **enteric microbes**. (Gardner 1987)

Five-sixths nephrectomy in rats leads to increased azotemia, causes cysts to develop in the remaining parenchyma. Cyst formation is enhanced by feeding the animals a high protein diet. (Kenner 1985)



Hormonal Factors

Kidneys from fetal mice in organ culture:

Hydrocortisone promotes cyst formation via increased activity of **Na⁺/K⁺-ATPase**. Cysts develop in the proximal tubule, regress when hydrocortisone is removed from medium. (Avner 1987)

Aldosterone and **hypokalemia** stimulate tubular cell proliferation, adenoma resection in humans has been shown to result in cyst regression. (Torres 1990)

Epithelial cells from normal human renal cortex (NHK) cultured in gelled type I collagen matrix. Cyst formation depends on:

Epidermal growth factor (EGF) and **insulin** .

Adenylate cyclase stimulants leads to induction and growth of cysts (Neufeld 1990)



Renal Cell Cancer - Risk Factors

Cigarette smoking doubles the risk of RCC

Obesity: increasing body weight linear relationship with increasing risk

Occupational exposure: cadmium, asbestos, trichloroethylene: 1-2x risk

Phenacetin-containing analgesic

Genetic factors: tuberous sclerosis, VHL disease

Hypertension, prior radiation, sickle cell disease

Acquired cystic kidney disease: ~100 fold increased risk



Renal Cell Cancer in ESRD/ACKD

Usually develops after 8-10 years of dialysis

Occurs in 4-7% of dialysis patients

M:F ratio 7:1

Larger cysts leads to increased kidney size > increased risk of transformation (kidneys > 150g are 6x more likely to contain carcinoma than smaller size kidneys)

Clear cell RCC is much less common as is its associated chromosome 3p deletions in sporadic forms.

Seems to have lower metastatic potential

May not always be related to acquired cystic disease



Renal Cell Cancer in ESRD/ACKD

Serum **hepatocyte growth factor (HGF)** increases as renal failure progresses, higher in pts on dialysis. (HGF mRNA and HGF protein, along with c-met protein upregulated in patients with RCC.)

Proto-oncogen C-Jun is activated in atypical hyperplastic proliferative cells in ACKD and plays a role in RCC carcinogenesis.

Anti-apoptotic **Bcl-2** over-expression may also have a role in tumor development

High proliferative activity of cyst epithelia in ACKD suggests, that these **cysts may be RCC precursors** (Nadasdy 1995)



Histology of RCC in ACKD (Tickoo 2006)

Common Variants ~40%

Clear Cell Carcinoma: ~18% in ACKD vs 70-80% of RCC in general population

Papillary RCC ~ 15%, over represented in ACKD.

Chromophobe RCC ~8%

New ACKD Associated Variants ~60%

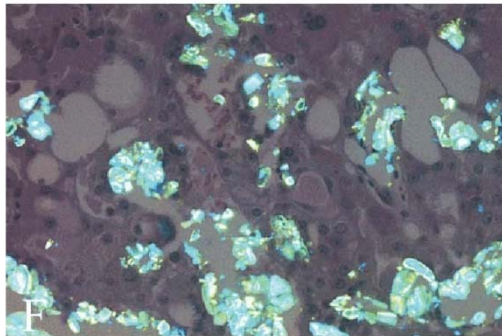
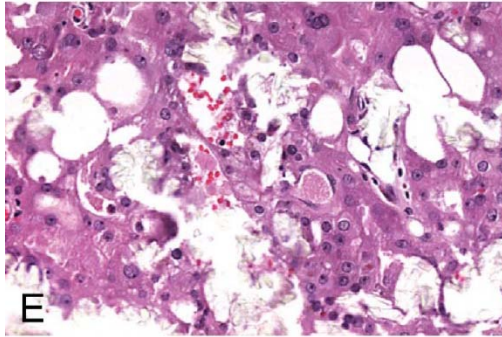
Acquired cystic disease (ACD) associated RCC: comprises ~36% of the dominant tumors in ACKD kidneys, not found in ESRD w/o cystic changes.

Clear cell papillary renal cell CA of ESRD: May occur in ESRD with or without ACKD. ~22% of dominant tumors in ACKD.

Abundance of **oxalate crystal deposition**, unique feature to renal cancer occurring in ESRD and ACKD.



Calcium Oxalate in ACKD associated RCC



Serum oxalate increases when **GFR < 25 mL/min**
➤ **increased deposition.**

Immunoprofile of the CaOx+ RCCs : pronounced expression of markers for proximal tubular differentiation.

➤ **proximal tubular differentiation** may play a crucial role in promoting **intratumoral CaOx deposition.**

In physiologic condition nephrocalcin, osteonectin, FK506-binding protein decreases CaOx crystals, some of which are localized to renal proximal tubules. **Nephrocalcin is shown to be decreased in ESRD associated RCCs.**



Calcium Oxalate in ACKD associated RCC

CaOx may cause:

- cell necrosis or apoptosis at higher concentration
- formation of reactive oxygen species
- inhibit several cytosolic enzymes.
- 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.



Screening for RCC in ACKD - Decision Analysis by Sarasin 1995

Estimated prevalence of ACKD in dialysis population: 35% - 95%. 13% ACKD at initiation of dialysis

Incidence of renal CA in ACKD: 1-7%, 3-6% pts w/ ACKD will develop RCC mean time on HD of 5 yrs

Incidence of renal cancer in HD pts free of ACKD: 0.6%

RCC, Clinical staging and mortality: data from non-uremic population with clear cell RCC.

Risk of radical nephrectomy: operative mortality rates for renal CA w/o mets 0.5-6%, up to 10% in pt w/ mets.

Perioperative mortality of ESRD pts undergoing general surgery: 3.9%

Imaging procedures CT > US, assumed that tests for cysts and renal CA have perfect specificity.

ESRD related mortality (USRDS) : 20y beginning RRT has avg life expectancy 25yrs/ 58y - 5yrs / 80y - 1.8yrs



Decision Analysis by Sarasin 1995 - Result

A patient with a 25-year life expectancy at the age of 20 can prolong life expectancy by 1.6 years by screening.

However, a patient with a life expectancy of only 5 years at the age of 58, **prolongs life by only 4 to 5 days** by screening.

Screening is not supported for all dialysis patients, however screening is valuable for patients in good general health with a good life expectancy.



Thank You!

