Translocation Renal Cell Carcinomas

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Kidney cancer is not a single disease

- Clear cell (75%)
- Type 1 papillary (10%)
- Type 2 papillary (5%)
- Chromophobe (5%)
- Oncocytoma (5%)
- Microphthalmia-associated transcription (MiT) family translocation kidney cancers (TFE3, TFEB, and MITF) (5%)
Kidney cancer is not a single disease

Distinct histology, a different clinical course, respond differently to therapy, caused by mutations in different genes

MiT family of transcription factors

TFE3, TFEB, MITF

Sporadic

Inherited
Papillary Kidney Cancer
t(X;1)(p11.2;q21.2) Translocation Observed in Human Papillary Kidney Cancer
The breakpoint region on the X chromosome

Fig. 1. Partial karyotype of the cell line UOK124 illustrating the rearrangements involving chromosomes X and 1. The karyotype contained a normal chromosome 1 but no normal X. The der(1) and the der(X) result from the t(X;1)(p11.2;q21.2) that is associated with papillary renal cell carcinoma and the der(1)del(1)(p31)t(X;1)(p11.2;q21.2) is thought to be derived by deletion following the duplication of the der(1) chromosome. The arrows indicate the position of the translocation breakpoints.

Shipley JM, Cytogenet Cell Genet 1995;71(3):280-4
Xp11.2 Translocation/TFE3 Fusion
Renal Cell Carcinoma

• Several different translocations involve chromosome Xp11.2, all resulting in fusions of the TFE3 gene

• First TFE3 fusion was described in 1996
• The t(X;1)(p11.2;q21.2) translocation in papillary renal cell carcinoma fuses a novel gene PRCC to the TFE3 transcription factor gene

Translocation Renal Cell Carcinomas
Microphthalmia Transcription Factor (MITF)-Associated (MiT) Tumors: Evolving Entity

• A family of transcription factors that are associated with rare malignancies:
  - translocation-associated renal cell carcinoma (tRCC; balanced translocation)
  - alveolar soft part sarcoma (ASPS)
  - clear cell sarcoma (CCS)
Predominantly affects children and young adults

Frequency
- 1-1.6% All renal tumors
- 15% RCC patients of <45 yrs old
- 20-45% RCC in children and young adults

Clinical features:
- painless mass
- hematuria
- asymptomatic
- present at advanced stage (ASPL-TFE3, PSF-TFE3 carcinoma)
- lymph node involvement
Xp11.2 translocation-associated RCCs

- Female: male ratio 2:1 and African Americans
- History of chemotherapy
- Sickle cell trait
- Hemihypertrophy of the face
- Saethre-Chotzen syndrome
- Cryptorchidism
- Coccygeal teratoma
Generally cortical or subcapsular, well-circumscribed lesions

Xp11.2 translocation-associated renal cell carcinomas
Abundant clear cytoplasm, mimicking clear cell RCC
May show marked focal cytological atypia and pleomorphic giant cells
May have well-developed papillae, mimicking papillary RCC
Abundant eosinophilic cytoplasm and high nuclear grade arranged in large nests with a delicate, intervening vascular stroma
Typically exhibit strong nuclear positivity for the transcription factor E3 (TFE3) protein.
Transcription factor EB (TFEB) RCC
Polygonal cells abundant clear to eosinophilic cytoplasm, high nuclear grade arranged in nests with delicate, intervening vascular network
Micropthalmia Transcription Factor (MITF) Kidney Cancer

- TFE3 kidney cancer
- TFEB kidney cancer
- MITF kidney cancer
  - Kidney cancer and melanoma families
13 year old female

- 06-2011: pain in the right flank
- **CT scan**: right kidney mass infiltrating the right psoas. Other lesion in the lower part of the right kidney. Metastatic lesion (16x19 mm) in the inferior lobe of the right lung.
- 07-2011: IL-2 plus sorafenib (400 mg BID)
- Therapy stopped after 10 days for surgery
13 year old female with right flank pain
CT scan before surgery
06-2011

Right lung inferior lobe mass
Right kidney mass infiltrating psoas
Lesion in the lower part of right kidney
Management

• Right radical nephrectomy + lymphadenectomy + partial resection of the cava

• Clear Cell Carcinoma with Xp11.2 translocation/TFE3 gene fusions; Fuhrman grade III, thrombosis of renal and caval veins, pT3b, Stage IV
CT scan after surgery
08-2011
First line therapy

- **08-2011**: IL-2 (4MUI 5 days q14 days) + Sunitinib 37.5 (continuously dose)

- **10-2011**: Hypertensive crisis, proteinuria and edema hypothyroidism (TSH 40)

- Therapy stopped 2 weeks and restarted with a dose reduction: with IL-2 (2MUI 5 days q14 days) + Sunitinib 25 (continuous dose)

- **12-2011**: IL-2 stopped, Sunitinib 25 mg continued
Recurrence 7 months later
CT scan 03 2012

6x3 cm mass englobing and infiltrating the vena cava, splenic artery, attached to the pancreas
Second line therapy

- 03-2012: Sorafenib 400 mg BID

- 07-2012: Sorafenib stopped; GI toxicity and HFS

- After 1 week therapy restarted with dose reduction (400 mg daily)
Best response to Sorafenib (6 months)

- MRI 03-2012
- MRI 09-2012

Reduced size and signal intensity of the retroperitoneal mass. Porto-cavale LN stable. Slight increased quota in the inferior vena caval reconstruction
Recurrent Disease: 12-2012

Retroperitoneal mass (5.5 cm x 4)
Englobing the vena cava, extending to the liver

Mesenteric, para aortic, diaphragmatic LNs
Second and Third line therapies

- 12-2012: After progression, Sorafenib rescaled to 600 mg daily with mild intolerance (diarrhea G1)

- Not eligible for Anti-PD1 study due to age

- 01-2013: Disease progression
  Started Sunitinib 25 mg (4/6 weeks) + Axitinib 5mg /day
Slight reduction retroperitoneal mass (27 vs 30 mm) and increase in the fluid component, stable left paraortic and porto-cavale LNs, reduction in the peri caval mass.
Kidney Cancer is a Metabolic Disease
Kidney cancer is not a single disease

• Thank you for your attention