ACCME/Disclosures

The USCAP requires that anyone in a position to influence or control the content of CME disclose any relevant financial relationship WITH COMMERCIAL INTERESTS which they or their spouse/partner have, or have had, within the past 12 months, which relates to the content of this educational activity and creates a conflict of interest.

Dr. Przybycin declares that he has no conflict(s) of interest to disclose.

- 48 year-old woman
- Kidney mass
Diagnosis

- Renal cell carcinoma, unclassified type, with features suggestive of Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC) Syndrome-associated Renal Cell Carcinoma

Surgeon response

- “...Thanks.”
- “...Thanks...Were the margins negative?”
- “...Thanks...Can you take pictures and send to my fellow?”
- “Thanks. We’ll send her for genetic counseling.”
Sequencing for Fumarate Hydratase mutation

- Tier 1 (hotspot)
  - Negative for FH mutation
- Tier 2 (remainder of coding regions of FH)
  - Heterozygous for deletion in FH

Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome (HLRCC)

- Autosomal dominant syndrome
- Germline mutations in one allele of fumarate hydratase (FH) gene (1q42.3-q43)
  - Biallelic germline mutations of FH: Fumarase deficiency

HLRCC syndrome clinical manifestations

- Cutaneous leiomyomas (penetrance 75-90%)
- Bulky uterine leiomyomas (penetrance 75-100% of women)
- Renal cell carcinoma (solitary; penetrance 20-30%)
HLRCC Syndrome-associated RCC

- Merino et al, AJSP 2007
- 40 tumors (38 patients) from HLRCC families with proven FH germline mutations
  - Characteristic nuclear features
  - Variable architecture
  - Unilateral and solitary
  - High stage, poor prognosis

Papillary RCC

Clear cell RCC
Clear cell RCC (rhabdoid)

IHC as an aid to diagnosis

- Chen et al, AJSP 2014
- 9 tumors (9 patients)
  - Detected by morphology
- ↑fumarate → succination
- High stage, poor prognosis, unilateral and solitary, variable architecture, limited clinical history

2SC expression: FH mutation

- Diffuse 2SC expression (nuclear+cytoplasmic) correlates with FH mutation and is not seen in other tumors with suggestive nuclear features

FH-deficient RCCs

- Trpkov et al, AJSP (epub)
- Screened 124 tumors (118 patients)
- High stage, poor prognosis, unilateral and solitary, variable architecture, limited clinical history
- FH-/2SC 2+
  - Correlates with FH mutation
  - Highly specific
  - 24/124 (19%) were FH-deficient RCC
  - 8/23 (35%) had known HLRCC
FUMARATE HYDRATASE
S-(2-succino)-cysteine (2SC)

Photos courtesy K. Trpkov

Architectural variety

Chen et al. AJSP 2014
Trpkov et al. AJSP 2016

Screening cutaneous leiomyomas

Buelow et al, AJSP (epub)

HLRCC-associated RCC

- Challenges and opportunities
  - Incomplete clinical history
  - Solitary, unilateral masses
  - Highly aggressive disease
  - Variable architectural patterns
  - ? Multiple therapeutic targets
Thank you