New Frontiers in Pathology

Case 1

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Clinical History

65 Y male, pelvic peritoneum biopsy
(Status post radical cystectomy at outside institution)
CK Cocktail

GATA 3

p63

PDL1 IHC (Dako 22C3)
No expression
CPS <10
Diagnosis: Plasmacytoid Urothelial Carcinoma
Plasmacytoid Urothelial Carcinoma (UC)

- Rare variant of urothelial carcinoma (1-5% of all UC), recognized by the 2016 WHO classification.
- Includes signet ring morphology lacking extracellular mucin and diffuse variants.
- Most common clinical presentation is hematuria.
- Composed of discohesive malignant cells resembling plasma cells and/or monocytes.
- Most cases reported as signet ring cell carcinoma of bladder (and not associated with extracellular mucin) are considered within spectrum of plasmacytoid UC.
Plasmacytoid UC: Gross

Edematous mucosa
Thickened bladder wall “linitis plastic-like”
Mass lesion may be noted

Tumor involvement likely to be more extensive than what is visualized on luminal aspect, cystoscopy/TUR
Plasmacytoid UC: Histology

• Discohesive oval to round cells with moderate to abundant amphophilic to eosinophilic cytoplasm & eccentrically placed nuclei that resemble plasma cells.

• Neoplastic cells may show vacuoles or form signet ring cells with focal intracytoplasmic mucin.

• Plasmacytoid cells are predominantly monotonous (usually 3 times larger than a lymphocyte) but larger cells with more atypia/pleomorphism can be noted.

• Sheet-like growth, pattern-less single-cell infiltration, small clusters or cords (simulating lobular carcinoma of the breast).
Plasmacytoid UC: Histology

Three morphologic groups

- **Classic**: Resembles invasive lobular carcinoma; plasmacytoid, monocytoid and signet ring; 2-3 times larger than lymphocyte

- **Pleomorphic**: Larger cells (4 times size of a lymphocyte); subset of cells may show prominent atypia mimicking rhabdoid cells; usually seen in association with classic morphology

- **Desmoplastic**: Prominent desmoplastic stromal response; many cells were pleomorphic while some were classic

Distinct survival outcomes
Desmoplastic variant: worst outcome
Classic morphology

Pleomorphic morphology
Pleomorphic morphology with marked atypia reminiscent of rhabdoid cells

Desmoplastic with signet ring cell morphology
Plasmacytoid UC

- Concomitant conventional urothelial carcinoma may be present (surface or invasive component)

- Amount of plasmacytoid/signet ring cells vary (Median 25%)

- Other divergent differentiation seen in about 30% cases

- CIS present in less than half (43%) cases
Plasmacytoid UC: Immunoprofile

- Positive with keratins {CK cocktail, CK 7 (85-90%), CK 20 and 34βE12}
- **GATA 3 positive (80-90%)**
- P63 positive (45-65%)
- CD 138 positive
- Uroplakin II positive in a subset of cases (33%)
- **ER and mammogobulin negative**
- No aberrant (nuclear) Beta-catenin expression
- GCDFP-15, PR and CDX2 positive in a small subset of cases (13-24%)
Plasmacytoid UC: Immunoprofile

- E-cadherin protein expression lost in a little over 50% cases

E-cad Negative & E-cad Positive Plasmacytoid UC cases

(desmoplastic variant was enriched for retaining E-Cadherin)
Plasmacytoid UC with desmoplastic features and retained E-Cadherin expression
Plasmacytoid UC: Molecular features

• Truncating somatic, loss of function mutations (common) and hypermethylation (rare) of CDH 1; results in E cadherin loss by IHC

• No germline CDH 1 mutation is noted

• Chromosome 9 commonly aberrant (deletion of chromosome 9p21 in 60% cases)

• FGFR mutations controversial; more data needed
Plasmacytoid UC: Staging and Prognosis

- Plasmacytoid UC are likely to be diagnosed at an advanced stage of presentation.
- Vast majority show high stage with nodal metastasis (85% and 72% cases) were pT3/pT4 and N2/N1 respectively.
- Upstaging pT1 tumors on TUR to pT2 or greater is common (40-80%).
- High rates of positive margins (soft tissue and ureter) on cystectomy (28-32%) compared to conventional UC.
- Desmoplastic variants enriched in pT3 and pT4 categories as well as positive margins (compared to classic and pleomorphic phenotype).
- Poor outcome with high rates of recurrence and death; higher mortality likely due to high proportion of advanced stage tumors at presentation.

Perrino et al Hum Pathol 2019, Sood et al arch Pathol Lab Med 2018
Plasmacytoid UC: Peritoneal spread

- Plasmacytoid UC show a predilection to spread along the peritoneum; **33% show peritoneal involvement at presentation.**
- Pelvic peritoneal infiltration, as seen in this index case, can be **detected by imaging** as thick sheets along fascial planes and is considered as a characteristic imaging finding.
- Recurrence as peritoneal carcinomatosis is seen in approximately **12%** of cases.
Plasmacytoid UC: Differential diagnosis

• Hematolymphoid malignancies (plasmacytoma/lymphoma)
  - CD138 is not a discriminator for plasmacytoma (rare in urinary bladder, express MUM1)
  - Lymphomas: Positive with lymphoid markers.

• Lobular carcinoma of breast
  - ER and mammaglobulin positive
  - GATA 3, PR, E-cadherin and GCDFP-15 of limited utility

• Signet ring adenocarcinoma: Includes cases with signet ring cells within extracellular mucin
  - Mets/direct extension from GI tract (widespread dissemination, no conventional UC)
  - CDX2 of limited utility

• UC with rhabdoid features
  Rare variant, prominent pleomorphic cytology, association with sarcomatoid divergent differentiation
Urinary bladder: Metastatic lobular carcinoma of breast
Plasmacytoid UC in fallopian tube
Plasmacytoid UC: Treatment

- Aggressive approach to therapy recommended by NCCN
- Upstaging at radical cystectomy to locally advanced and metastatic disease is common
- Radical cystectomy recommended for Loco-regional disease
- Chemotherapy (neoadjuvant or adjuvant setting) appears to have little effect
- Immunotherapy (PDL1 Dako 22C3 clone), attempted in subset, short lived response
- Recent studies appear to suggest that desmoplastic variant appears to be most aggressive (median survival 10 months); however data is limited and further studies are required

**Dako PD-L1 22C3(Keytruda/pembrolizumab)**
- PDL1 Expression: CPS ≥ 10 required for therapy
- No expression (Combined Positive Score, CPS<10)

**CPS**: PDL1 positive cells (tumor cells, lymphocytes, macrophages) / total number of viable tumor cells x 100
Plasmacytoid UC: Take-away

- Rare variant of UC with poor outcome and potential aggressive management
- **Critical to identify this variant and mention (quantify) in pathology reports**
- Unique clinical presentation, morphology, immunoprofile and molecular features
- Signet ring cell morphology with intracytoplasmic mucin is part of spectrum of plasmacytoid UC
- Vast majority of positive with GATA 3 in addition to cytokeratins; if lobular carcinoma of breast in DD, positive mammogluglin and ER support the diagnosis in the right clinical context
- Shows E-cadherin loss by IHC and somatic CDH 1(Cadherin-1) mutation; however e-cadherin positive cases also reported with poorer prognosis
- FS ureter and urethra margins requires careful evaluation; Plasmacytoid UC has propensity for positive margins and to infiltrate soft tissue around urothelium
- Recent studies appear to suggest that desmoplastic variant appears to be most aggressive (median survival 10 months); however data is limited and further studies are required
Thank You

Wow! That was a great lecture!

I'm so confused.

GREAT MOMENTS IN TEACHING

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