Molecular Profiling and Identification of Targetable Biomarkers in Plasmacytoid Urothelial Carcinoma of the Bladder

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Introduction

Muscle-invasive bladder carcinoma constitutes about 25% of all newly diagnosed bladder cancers; a stage associated with markedly higher mortality and systemic spread risk. Plasmacytoid urothelial carcinoma (PUC) of the bladder is a rare, aggressive variant of urothelial carcinoma (UC). PUC is characterized by inactivating mutations or promoter hypermethylation of the *CDH1* gene, which leads to loss of E-cadherin expression and discohesive, infiltrative growth. However, the molecular landscape and actionable biomarkers in PUC remain incompletely defined.

Materials and Methods

We summarized biomarker results from seven tumors with a plasmacytoid component (six pure PUC; one mixed UC with 10% plasmacytoid morphology) and compared them with 12 cases of invasive bladder UC, NOS. We assessed HER2 expression by immunohistochemistry (VENTANA anti-HER2/neu 4B5). Strong, lateral/basolateral Her2 expression in ≥10% was scored positive (3+). We assessed PD-L1 using the 22C3 clone (Agilent). We considered a combined positive score (CPS) ≥10 positive. A comprehensive next-generation sequencing assay was used to explore genomic alterations, microsatellite status, and tumor mutational burden (TMB).

Results

Among 12 urothelial carcinoma cases NOS, *TP53* mutations and *TERT* promoter alterations were the most frequent findings (6/12, 50%). *TERT* alterations were predominantly C228T (n = 3) and C250T (n = 2), whereas the *TP53* mutations were molecularly heterogeneous. Other, recurrently altered genes included *FGFR3, ERBB2, ARID1A, KDM6A, RAD51, SLX4*, and *LATS1*, highlighting substantial genomic diversity across the cohort. Molecular profiling data for seven PUC cases are shown in the table below.

Case/Diagnosis	HER2 status	Genomic biomarkers	I-O Biomarkers
Case 1 (PUC)	Score 3+	*BRCA2, PIK3CA, TERT, RHOA*	TMB: 16 mutations/Mb PD-L1 negative, MSS
Case 2 (PUC)	Score 2+	*ERBB2, TERT*	TMB: 11 mutations/Mb PD-L1 negative
Case 3 (Mixed, plasmacytoid component 10%)	Score 2+	*ARID1A, BAP1, KDM6A, RAD50, STAG2, KMT2C*	MSS TMB: 15 mutations/Mb
Case 4 (PUC)	Score 3+	*ATM, BAP1, ERBB2, ERBB3, ERCC2, FBXW7, SMARCA4 TERT, KMT2C*	Microsatellite stable (MSS) TMB: 15 mutations/Mb, PD-L1+ (CPS 80)
Case 5 (PUC)	Score 0	*CDK12, POLE, RB1, TP53, TERT, CDH1, KMT2C, KMT2D, RHOA*	MSS, TMB: 9/mutations/Mb
Case 6 (PUC)	Score 2+	*EP300, TERT, TP53, RB1, ERBB4* (amplification)	MSS, TMB: 7/mutations/Mb PD-L1+ (CPS 30)
Case 7 (PUC)	Score 0	*FGF3, FGF4* (amplification)	PD-L1 positive (CPS 20)

*PUC = Plasmacytoid urothelial carcinoma; UC = Urothelial carcinoma; I-O = Immuno-Oncology; Mb = Megabase; MSS = Microsatellite stable; TMB = Tumor mutational burden; CPS = Combined positive score; PD-L1 = Programmed death ligand 1.

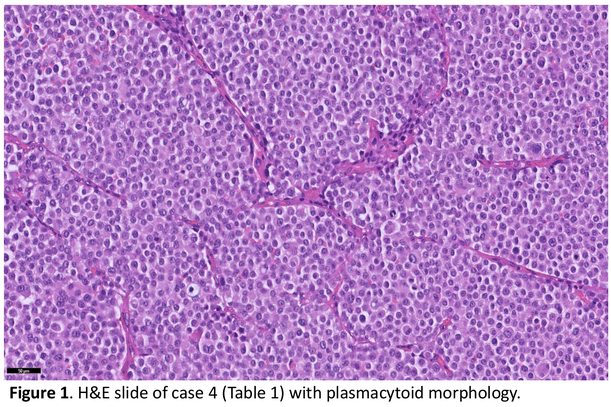

Figure 1. H&E slide of case 4 (Table 1) with plasmacytoid morphology.

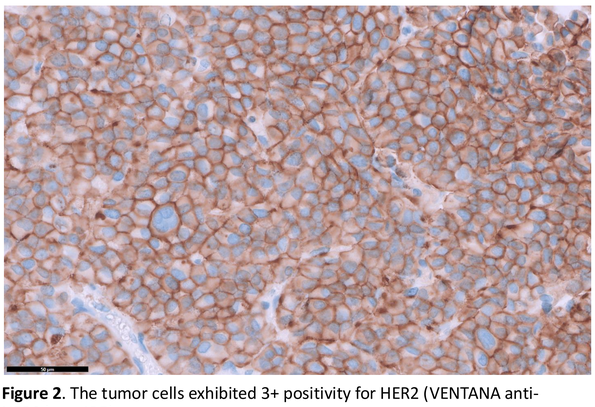

Figure 2. The tumor cells exhibited 3+ positivity for HER2 (VENTANA anti-HER2/neu 4B5).

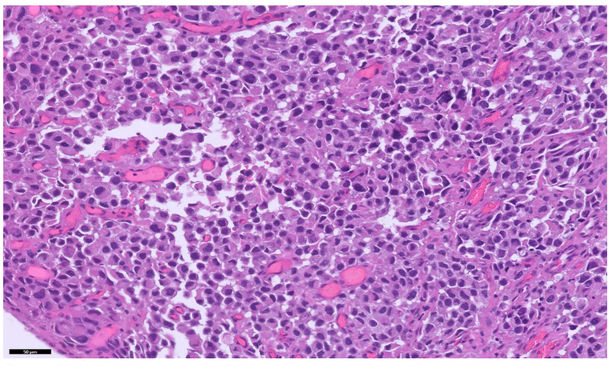

Figure 3. H&E slide of case 1 (Table 1) with plasmacytoid morphology.

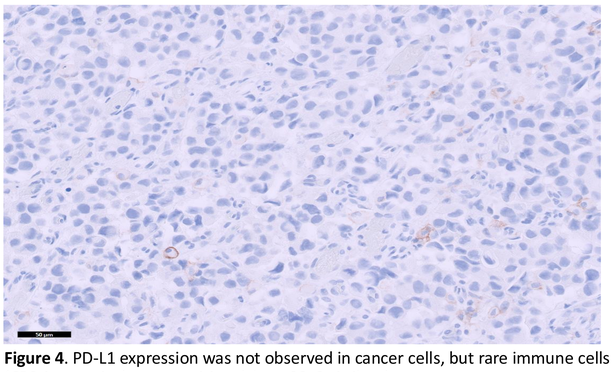

Figure 4. PD-L1 expression was not observed in cancer cells, but rare immune cells (CPS 1, negative) were positive. (clone 22c3, Agilent).

Conclusions

This study highlights biomarker heterogeneity in PUC, while strong (2-3+) HER2 expression offers potential benefits from the recently developed antibody-drug conjugates (ADC). PD-L1 expression and TMB-H are potential targets for I-O therapy in microsatellite stable cancers.

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Conflict of Interest: None to declare.