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Uterine Papillary Serous Carcinoma and Endometrioid Carcinoma: Novel Immunostains with Respect to Clinical-Pathologic Factors Predicting Survival

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Background:Uterine papillary serous carcinoma (UPSC), also known as type II endometrial carcinoma, is an uncommon aggressive variant of endometrial carcinoma [1, 2]. Its tumorigenesis, as well as its clinical risk factors differ from the commonly occurring endometrioid carcinoma (EC) [3-5]. Typical pathologic factors also differ. Even with minimal myometrial invasion, lymph-vascular space invasion or tumor limited to polyps, UPSC has been found to be associated with widespread metastasis, recurrence, and poor survival [6]. Since UPSC may be difficult to differentiate from high grade endometrioid carcinoma, particularly in mixed carcinomas, immunohistochemical techniques may facilitate such diagnoses, and even potentially serve as prognostic factors. Three novel proteins, L523S (also known as KOC—K homology domain containing protein over expressed in cancer), an oncofetal RNA-binding protein; O8E (also known as CRxA-01), a novel protein involved in T-cell regulation; and WT1 (Wilm's Tumor) a tumor suppressor gene, have shown positive expression in various cancers [7-13]. Their expression and prognostic implication in UPSC is unknown.

Objectives: To evaluate L523S, O8E and WT1 expression in UPSC and EC. To correlate clinical-pathologic factors to these staining patterns.

Methods: A search of the University of Massachusetts Medical Center database was performed for UPSC from 1998 to 2003, and for EC from 2002-03. The UPSC group consisted of 31 patients, and EC group of 63 patients. All cases were reviewed by the authors EK and BX. A tissue block containing the best representation of UPSC and EC was selected for each case, and stained for L523S, O8E, and WT1, on a Dako autostainer, per protocol [13]. Histologic scoring of all stains were conducted by one examiner, EK. A retrospective chart review of each patient was performed to extract clinical and pathologic variables. Staining outcomes were tested using a Fisher's Exact test, with significance level determined at $\alpha=0.05$. Demographic variables of normal distribution were tested using a heteroscedastic T-test (2-tail, $\alpha=0.05$).

Results: Significant differences were found for age ($p=0.004$) and BMI ($p=0.016$) between UPSC and EC. Racial distribution, gravidity, and parity were similar. EC patients had greater use of hormone replacement therapy, oral contraceptives, and cigarette smoking. They also had greater occurrence of diabetes (38.33% vs 17.34%) and family history of breast cancer (33.93% vs 23.08%) and gynecologic cancers (30.36% vs 19.23%), although UPSC patients had a greater occurrence of personal history of breast cancer (21.42% vs 14.75%). Overall, UPSC had a greater distribution of higher-staged cases. The stage distribution of UPSC and EC were as follows: Stage I UPSC (10/26, 38.46%) and EC (48/63, 76.19%); Stage II UPSC (3/26, 11.54%) and EC (5/63, 7.94%); Stage III (10/26, 38.46%) and EC (10/63, 15.87%); Stage IV UPSC (3/26, 11.54%) and EC (0/64, 0%). UPSC patients had higher rates of recurrence (50% vs 7.01%). Significantly more UPSC stained positive for L523S ($p<0.0001$) and WT1 ($p=0.0015$). There is a slight trend of higher surgical stage for UPSC L523S(+) cases versus UPSC L523S(-) cases: L523S(+) Stage I and II consisted of 7/17 (41.18%) cases, and L523S(-) of 5/8 (62.50%) cases. L523S(+) Stage III and IV consisted of 10/17 (58.82%) cases, and L523S(-) of 3/8 (37.5%) cases. Of the UPSC L523S(+) cases, 3 patients have expired, 2 of whom were staged as IIB and IIIA. Of the serous L523(-) cases, 2 patients have expired, staged at IIIA and IIIC. Of the endometrioid L523(+) cases, 2 were stage IA and one was of stage IB. For WT1, UPSC showed five positive cases, whereas no EC cases were positive. Of the UPSC WT1(+) cases, all were stage III, and three patients have expired. In contrast, staining for O8E did not significantly differ between UPSC and EC ($p=0.1851$).

Discussion: UPSC is an uncommon, aggressive variant of endometrial carcinoma. Similar to previous studies, UPSC is found in patients of greater age, and BMI, and less associated with diabetes, and hormone use. The higher rate of family history of breast and gynecological cancer in the EC group may reflect the hormone-positive nature of most EC tumors. However, it is unclear why UPSC patients had a greater percentage of breast cancer. The higher rate of expired UPSC patients may reflect the aggressive nature of the disease, or in this study, a longer duration of follow-up. The staining pattern most significantly differed between the serous and endometrioid groups with L523, suggesting that it may be a tool to aid pathologist's diagnosis of UPSC, particularly in mixed cases. Additionally, L523 may be a marker for worse prognosis in UPSC cases. However, the study was limited by the small number of UPSC cases. WT1 also significantly stained more serous cases compared to endometrioid cases. However, the absolute number of serous WT1(+) was quite small. It is unclear if these cases consisted solely of UPSC with metastasis to the adnexa, or if these cases were actually dual ovarian and endometrial primaries, or potentially even ovarian carcinomas that had metastasized to the uterus. O8E staining did not significantly differ between UPSC and EC, and thus would not aid in the histologic differentiation between the two. Inherent limitations in this study included loss-to-followup, incomplete charts, follow-up with providers outside of this hospital, lack of abundant tissue and loss of tissue blocks. Further study would include increasing the number of UPSC cases, as well as including EC cases diagnosed during the same time frame as UPSC cases.

Conclusions: UPSC significantly expresses L523S in comparison to EC. Positive staining of UPSC cases may be associated with higher stage and worse prognosis. Further investigation of additional UPSC cases may clarify the utility of this novel immuno-marker.

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