Correlation of Tumor ARID1A Mutations, BRAF V600E Mutations and Microsatellite Instability in Sporadic and Tamoxifen-Associated High Grade Endometrial Cancer

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Tamoxifen (TAM), a selective estrogen receptor modulator used in breast cancer therapy, has partial agonist activity on the endometrium and increases the risk for developing type II endometrial carcinomas. While the mechanism of TAM induced tumorigenesis is unknown, several genetic alterations have been identified in endometrial carcinoma. Recently, genetic instability in the hMLH1 gene has been linked to BRAF V600E mutations in colorectal carcinomas. We performed ARID1A mutation, BRAF V600E mutation, and MSI analysis on endometrial tumors with a history of TAM use, and compared them to matched controls. Tissue microarrays (TMA) were constructed from tissue cores of 13 high-grade endometrial carcinomas (malignant mixed mullerian tumor (MMMT)=7, serous=5, grade III endometrioid=1) arising in patients treated with TAM and 13 matched controls. The TMAs were examined with immunohistochemistry (IHC) for the loss of expression of ARID1A, and the expression of the mutation specific BRAF V600E antibody VE1. BRAF V600E mutation bearing colonic adenocarcinomas were used as controls. An ovarian clear cell carcinoma was used as the ARID1A control. For MSI evaluation, fluorescent multiplex PCR-based MSI Analysis System with 5 consensus markers was applied. Immunohistochemical analysis for the BRAF V600E mutation showed weak, focal staining in 3 serous carcinomas of the TAM group, all considered negative. All other cases showed no BRAF V600E antibody expression and all retained ARID1A staining. MSI analysis of the TAM treated cases revealed no MSI-H tumor and 1 MSI-L serous carcinoma (7.7%). In the control group, 1 MSI-H MMMT (7.7%) and 1 MSI-L serous carcinoma (7.7%) were found. There were no significant differences in MSI between the TAM-associated and the sporadic tumors. Both groups revealed no evidence of BRAF V600E or ARID1A mutations. Our data indicate that ARID1A and BRAF V600E are not the target genes for abnormal MMR protein expression in either sporadic or TAM-associated endometrial carcinoma.