Paired germline and somatic mutations in VHL in a patient with recurrent endometrial cancer: driver for therapeutic targeting?

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Introduction: The tumor suppressor *VHL* gene is associated with autosomal dominant von Hippel-Lindau syndrome, classically known to increase risks of renal cell cancers (RCCs), pancreatic neuroendocrine tumors, retinal and CNS hemangioblastomas, with sensitivity to HIF-1 inhibitors. Other mutations in the VHL gene can cause autosomal recessive familial erythrocytosis (ARFE), without increased risks of these cancers.

Case: We present a case of a postmenopausal Caucasian female with history of early-stage breast cancer at age 44 and then a high-grade papillary serous adenocarcinoma of the endometrium at age 53. Given her personal history of 2 cancers, with family history of throat cancer and leukemia in paternal second-degree relatives, as well as unknown maternal history, she underwent a germline testing (sent as a 47-gene panel), which ruled out mutations in *BRCA1* or *PTEN*, but detected a heterozygous pathogenic variant in *VHL* (c.598C>T [p.Arg200Trp]), reportedly associated with ARFE, with classic VHL syndrome in only 1 family in the literature (including the VHL Alliance compilation), and seen in 1/20 individuals with Chuvash heritage. In addition, from a genetic counseling perspective, offering cascade testing for this germline variant to offspring is addressed, the tracking of which may assist surveillance for family members.

Upon progression of her disease, and difficulty tolerating chemotherapy, genomic sequencing of the original tumor was sent, and identified the same alteration in *VHL* (VAF 74%), as well as microsatellite stability, low tumor mutational burden (TMB) at 6 mutations/Mb, *ERBB2* amplification, and alterations in PIK3CA and TP53, the latter not seen in her germline testing. There were no other actionable targets at that time, but recommendation for participation in other early phase clinical trials overlapping with mTOR pathway was suggested for multiple tumor types. The patient succumbed due to multifactorial conditions in late 2019.

Discussion: Mutations in *VHL* are rare in endometrial cancer (Xu *et al*, Int J Gynecol, 2011), and have been identified in only 0.3% of all 12,895 endometrial carcinomas and 0.3% of 3,221 papillary serous carcinomas in the Foundation Medicine database. Belzutifan, a HIF-2a inhibitor is now FDA approved since 2021, for use in patients with VHL related malignancies. Given the high tumor VAF for VHL mutation, exceeding 50%, we pose the question as to whether this patient with this inactivating VHL mutation (for which experimental data has shown disruption of the hypoxia response pathway) would now have been eligible for further therapeutic intervention, and whether evaluating this pathway in endometrial cancer would now have clinical benefit.

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