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CHEK2 C1100del mutation associated with papillary renal cell carcinoma type II

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ABSTRACT

CHEK2 mutations have been noted in bone, brain, breast, colon, lung, thyroid, and prostate cancer. Although now reported in both clear cell and non-clear cell renal cancer, we have not found CHEK2 2 mutations reported in the papillary type II subtype (PRCC). Here, we report a 63-year-old female with a PRCC type II with a concomitant CHEK2 C1100del mutation, who is currently in complete remission three years post tumor resection.

1. Introduction

Renal cell carcinomas (RCC) are sub-classified as clear cell (ccRCC) or non-clear cell (non-ccRCC). Papillary RCC (PRCC) are one subtype of non-ccRCC, accounting for about 15% of all RCCs. PRCC is further subdivided into type I and type II morphology. Type I consists of small cells with pale cytoplasm and type II of large cells with eosinophilic cytoplasm. Type II PRCC has been considered more aggressive, although this remains somewhat controversial. Studies have now reported CHEK2 mutations in both clear cell and non-clear cell renal cancer.[1,2]

Here, we report what may be the first patient with PRCC type II and a CHEK2 C1100del mutation who is currently in remission over three years post resection.

2. Case presentation

A 63-year-old woman presented with right upper quadrant pain, attributed to biliary colic. Past medical history was significant for Hashimoto thyroiditis, dyslipidemia, gastroesophageal reflux, obstructive sleep apnea, interstitial cystitis, anxiety, osteoarthritis, and an extensive list of severe food and drug allergies. Family history was notable for maternal renal cancer (type unknown). Physical examination was completely unremarkable. Abdominal ultrasound revealed a right upper pole renal mass, confirmed by subsequent magnetic resonance imaging (MRI) and computed tomography (CT). The mass was exophytic, with no distant metastases identified. A robotic assisted laparoscopic right partial nephrectomy was performed followed by an unremarkable hospital course. Pathology identified a unifocal 3.2 cm tumor composed of distinct papillary architecture lined by cells with abundant eosinophilic cytoplasm and foamy histiocytes (see Figs. 1 and 2), PRCC type II, clinical stage pT1a with negative resection margins.

A molecular sequencing panel (Invitae, San Francisco, CA) detected two mutations: 1) a pathogenic heterozygous CHEK2 C1100del, and 2) a heterozygous POLE c.4169G > A of unknown significance. No other mutations were found in 82 other tested genes. During follow up surveillance, the patient had unremarkable sequential CT scans of the chest, abdomen, and pelvis over the next three years. Colonoscopy and breast imaging have also been negative.

3. Discussion

CHEK2 (Checkpoint kinase 2) is a tumor suppressor gene located on the long (q) arm of chromosome 22 at position 12.1. CHEK2 encodes the serine-threonine kinase CHK2 involved in DNA repair, cell cycle arrest, and apoptosis in response to DNA damage CHK2 protein acts as a tumor suppressor, regulating cell division and preventing cells from uncontrolled, rapid division. When DNA damage occurs, CHEK2 is activated via ATM-dependent pathways leading to phosphorylation of multiple substrates such as BRCA1, P53, CDC25A, and CDC25C.[2,3] Thus, any decreased level of tumor suppression caused by a CHEK2 mutation can induce an increased incidence of cancer.

CHEK2 mutations can be missense (I157T) or truncating (C1100del) mutations, with C1100del commonest. CHEK2 germline mutations have been linked with inherited cancer susceptibility.[3] Mutations in the

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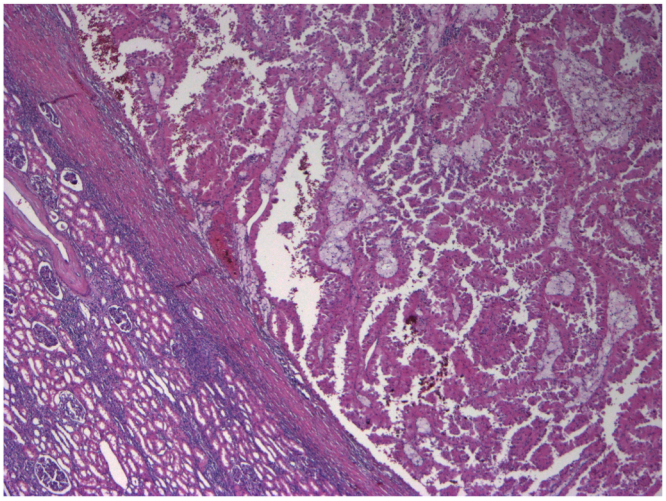

Fig. 1. The tumor is sharply demarcated from the adjacent benign renal parenchyma (left) and displays a prominent papillary architecture.
Hematoxylin and Eosin stain at 4x magnification.

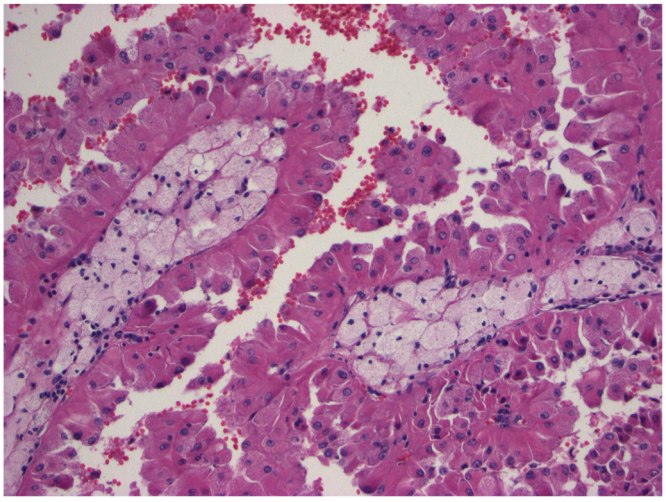

Fig. 2. The papillary fronds are lined by tumor cells with round vesicular nuclei, distinct nucleoli, and abundant brightly eosinophilic cytoplasm. Within the papilla are clusters of foamy histiocytes characteristic for papillary RCC, type II.
Hematoxylin and Eosin stain at 20x magnification.

CHEK2 gene have now been found in both hereditary and nonhereditary cancers of bone, breast, colorectal, gastric, glioblastoma, lung, melanoma, ovary, prostate, and thyroid.[3]

Huszno[2] in 2017 tested 43 ccRCC Polish patients by RFLP-PCR for *CHEK2* 1100delC, IVS2+1G →A (premature protein truncation) and missense variant (I157T) (substitution of an isoleucine for a threonine). They found the I157T variant in 3 (7%) patients, all with higher histologic grade (G3) and older. They did not find a patient with the *CHEK2* 1100delC variant.[2]

Carlo[1] in 2018 reported a cohort study of 254 patients with advanced RCC; 177 had ccRCC (69.7%), 74 had nccRCC (29.1%), and 3 (1.2%) had both. Germline mutations were identified in 41 (16.1%); 14 (5.5%) had mutations in syndromic RCC-associated genes (7 in *FH*, 3 in *BAP1*, and 1 each in *VHL*, *MET*, *SDHA,* and *SDHB*). The most frequent mutations were *CHEK2* (n = 9) and *FH* (n = 7). Of genes not previously associated with RCC risk, *CHEK2* was overrepresented in patients compared with the general population, with an odds ratio in RCC patients of 3.0 (95% CI, 1.3–5.8; $P = .003$); 8 of 177 (4.5%) patients with ccRCC and 2 of 74 (2.7%) with nccRCC had a CHEK2 mutation.[1]

Zlowocka-Perlowska[4] in 2019 genotyped 835 patients with invasive RCC and 8302 adult controls for 4 *CHEK2* founder alleles – 1 missense mutation (I157T) and 3 truncating mutations (1100delC, IVS2 + 1G > A, del5395). The I157T allele was present in 78 of 835 (9%) RCC patients and in 410 of 8302 (5%) of controls. A truncating mutation was present in 20 of 835 (2%) RCC patients and in 80 of 8302 (1%) controls.

4. Conclusion

We have not found CHEK2 mutations reported in the uncommon papillary type II RCC subtype. The patient reported here had a CHEK2 (C1100del) mutation and a PRCC type II, with excellent survival for three years post resection, and may be the first such patient reported.

Now, the PARP inhibitor olaparib (Lynparza) has received FDA-approval to treat men with metastatic, castration-resistent prostate cancer who have a mutation in CHEK2 or another gene linked to DNA damage repair.

Now, there is an ongoing phase II study of oral olaparib in metastatic RCC with an inactivating mutation in CHEK2 or other specified genes [ClinicalTrials.gov Identifier: NCT03786796].

As genetic testing becomes more frequently employed in RCC, genetic variants will likely be detected allowing better incorporation of targeted therapies.

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