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Renal Neoplasia in Cowden Syndrome

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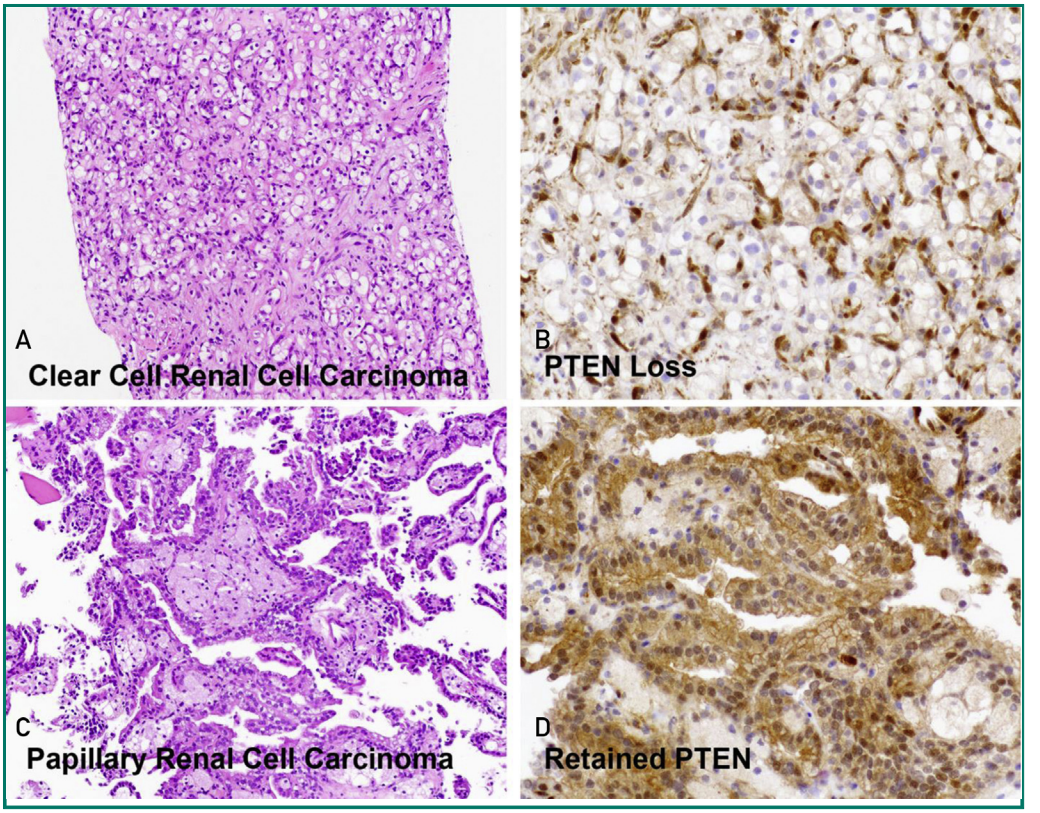
A 63-year-old man had been previously diagnosed with macrocephaly, a seizure disorder, intestinal ganglioneuromatosis, multiple hamartomatous colonic polyps, multinodular thyroid as well as multiple skin lesions (including facial trichilemmomas), lipomas, neuromas, and fibromas of the soft tissue. Germline testing revealed a heterozygous pathogenic *PTEN* alteration (c.389G>T) consistent with PTEN hamartoma tumor syndrome, specifically Cowden syndrome. He was on active surveillance for 2 right-sided renal masses (3.8 and 2.2 cm), which were biopsied. Histopathological examination revealed the larger tumor to be a clear cell type renal cell carcinoma (A) with loss of PTEN immunostain (B). The smaller tumor was diagnosed by pathology as a papillary renal cell carcinoma (C) with retained PTEN by immunohistochemistry (D).



This is an unusual situation. **However, if each tumor was from separate patients rather than from an individual known to have Cowden syndrome, which of the 2 renal tumors would be thought likely to be sporadic rather than occurring in the setting of Cowden based on the PTEN immunohistochemistry?**

a. Only the clear cell renal cell carcinoma
b. Only the papillary renal cell carcinoma
c. Both the clear cell type renal cell carcinoma and the papillary renal cell carcinoma
d. Neither the clear cell type renal cell carcinoma nor the papillary renal cell carcinoma

(see page 2809 for answer)

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Answer: **b. Only the papillary renal cell carcinoma**

Based on the immunohistochemical findings alone in the 2 tumors described, loss of PTEN expression in the clear cell type renal cell carcinoma may suggest that this tumor has loss of heterozygosity at the *PTEN* alteration locus while the papillary renal cell carcinoma exhibits retained expression of PTEN, suggesting that this may be a sporadically occurring tumor. Because of the limited nature of the biopsy material, molecular testing could not be performed to confirm immunohistochemistry findings in this exceptional case. Although the papillary renal cell carcinoma exhibits retained immunohistochemical expression of PTEN, this finding in the setting of a patient with Cowden syndrome raises the possibility that immunohistochemistry alone may not necessarily identify all *PTEN* alterations resulting in loss of function.

PTEN hamartoma tumor syndromes, secondary to pathogenic germline alterations of the *PTEN* gene on chromosome 10q, lead to a spectrum of hamartomatous overgrowth disorders including Cowden syndrome, Lhermitte-Duclos disease, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome.[1] In one study, the age-adjusted standardized incidence ratio of renal neoplasia in patients with pathogenic germline mutations of the *PTEN* gene was estimated to be 31.7 compared to the general population.[2] Pathology review of renal tumors from 8 such patients in this study revealed 6 papillary renal cell carcinomas and 2 chromophobe renal cell carcinomas, and immunohistochemistry revealed loss of PTEN expression in 7 (of 8) tumors (87.5%).[2] In another study, 4 patients with Cowden syndrome and renal neoplasia were identified: papillary renal cell carcinoma in 2 patients, clear cell type renal cell carcinoma in 1 patient, and bilateral chromophobe renal cell carcinomas in 1 patient.[3] Importantly, a second hit alteration involving loss of heterozygosity at the *PTEN* alteration locus was identified for all 4 patients in this study.[3] As mTOR inhibitors have been approved to treat renal cell carcinomas, these agents may be considered for patients with Cowden syndrome that have renal cell carcinomas with *PTEN* loss-of-function alterations.[3]

REFERENCES

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3. Shuch B, Ricketts CJ, Vocke CD, et al. Germline PTEN mutation Cowden syndrome: an underappreciated form of hereditary kidney cancer. *J Urol*. 2013;190(6):1990-1998.