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Original contribution

# Renal cell carcinoma with angioleiomyoma-like stroma and clear cell papillary renal cell carcinoma: exploring SDHB protein immunohistochemistry and the relationship to tuberous sclerosis complex☆,☆☆

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**Summary** Renal cell carcinoma (RCC) with angioleiomyoma-like stroma appears to be molecularly distinct from clear cell RCC; however, its relationship to clear cell papillary RCC remains debated. Recent studies have found that similar tumors sometimes occur in patients with tuberous sclerosis complex (TSC), of which 1 study found unexpectedly negative succinate dehydrogenase B (SDHB) immunostaining. We evaluated immunohistochemistry for SDHB in 12 apparently sporadic RCCs with angioleiomyoma-like stroma and correlated with clinical information for stigmata of TSC. Tumors were compared with a group of 16 clear cell papillary RCCs and 6 unclassified tumors with prominent stroma. With the exception of 1 unclassified tumor, all exhibited at least focal cytoplasmic staining for SDHB protein, often requiring high magnification and better appreciated with increased antibody concentration. Detailed history information was available for 9 of 11 patients with smooth muscle–rich tumors, revealing no stigmata of undiagnosed TSC. Electron microscopy performed on 1 of these tumors revealed mitochondria to be very sparse, potentially accounting for the weak immunohistochemical labeling for SDHB protein. Weak SDHB immunostaining may represent another shared feature of RCC with angioleiomyoma-like stroma and clear cell papillary RCC, likely due to sparse mitochondria, strengthening the possible relationship of these entities. Although smooth muscle–rich tumors have been recently reported in patients with TSC, absence of staining in tumors with this pattern may not be specific for TSC. In tumors with pale or clear cytoplasm, immunohistochemical staining for SDHB should be interpreted with caution as evidence of abnormality in the SDH pathway.


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## 1. Introduction

Renal cell carcinomas with angioleiomyoma-like stroma [1,2] and likely related entities renal cell carcinoma with smooth muscle stroma [3,4] and renal angiomyoadenomatous tumor [5,6] are thought to be immunohistochemically and molecularly distinct from clear cell renal cell carcinoma [2,7]. However, it remains debated whether these tumors should be regarded as variants of clear cell papillary renal cell carcinoma [8-10] because of the shared features of cytokeratin 7 and high–molecular weight keratin immunohistochemical labeling and lack of reactivity for α-methyl-acyl-coA-racemase, combined with absence of other defining genetic alterations [2,7].

Interestingly, 2 recent reports have noted a tendency to encounter a similar morphology in patients with tuberous sclerosis complex [11,12], of which 1 study found the tumors to be unexpectedly negative for succinate dehydrogenase B (SDHB) immunohistochemical staining [12]. We therefore sought to assess SDHB immunohistochemical staining in a cohort of apparently sporadic tumors with smooth muscle stroma to determine whether negative staining is consistently associated with this morphology or with tuberous sclerosis–associated tumors.

## 2. Materials and methods

A cohort of 12 renal cell carcinomas with angioleiomyoma-like stroma from 11 patients were selected for analysis, of which 10 tumors from 9 patients were previously reported [2] and 2 represent additional unpublished cases. These were compared with 16 clear cell papillary renal cell carcinoma tumors and 6 unclassified tumors with prominent stroma not fitting cleanly into a distinct category. The unclassified group included 1 tumor that upon review was interpreted as likely sarcomatoid renal cell carcinoma with the spindle-shaped cell component mimicking myoid stroma, 2 that had suggestive morphology and immunohistochemical phenotype but were shown to have chromosome 3p deletion using fluorescence in situ hybridization, 1 that had similar morphology and immunohistochemical staining pattern but was predominantly papillary (even more strongly resembling the tuberous sclerosis–associated morphology), and 1 that had borderline

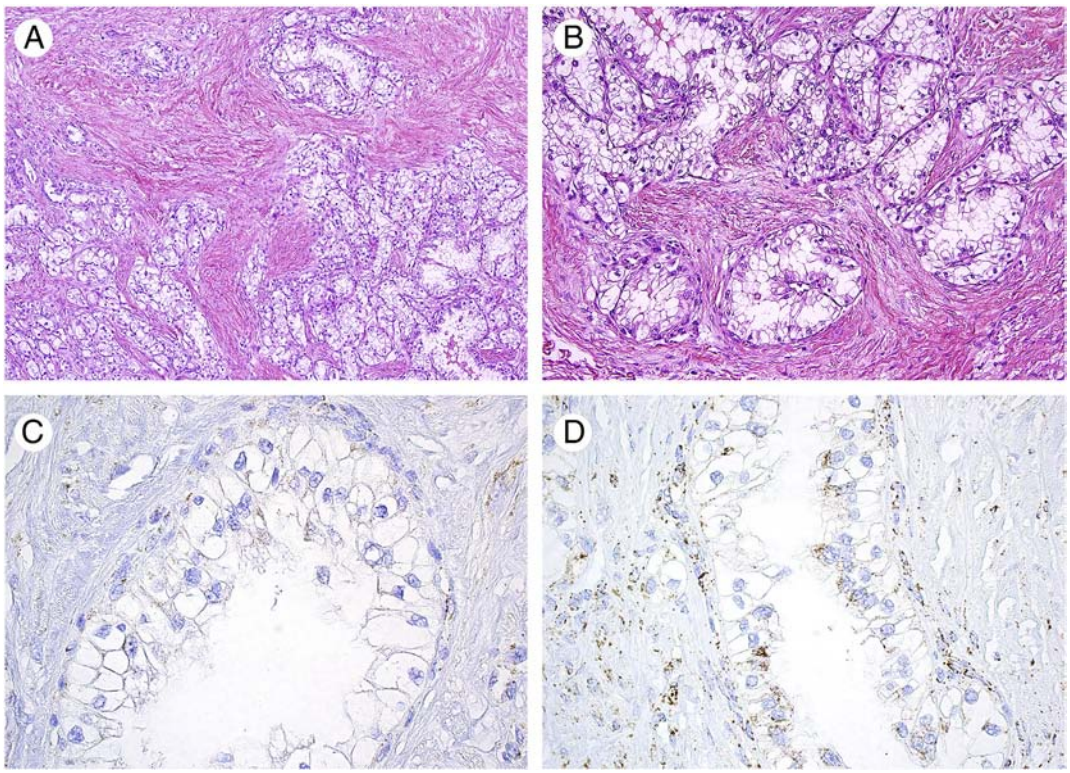


**Fig. 1** A, Renal cell carcinoma with angioleiomyoma-like stroma is composed of glandular structures dispersed in fibromuscular stroma, lined by cells with clear cytoplasm (hematoxylin and eosin, original magnification ×100). B, Higher magnification reveals nests and glandular structures with clear to eosinophilic cytoplasm in abundant muscular stroma (hematoxylin and eosin, ×200). C, Immunohistochemistry for SDHB performed at usual antibody concentration (1:100 dilution) appeared near-negative, although faint, focal cytoplasmic staining was observed (anti-SDHB immunohistochemical staining, ×600). D, Repeated analysis with increased antibody concentration (1:50) revealed sparse but recognizable cytoplasmic granules (anti-SDHB immunohistochemical staining, ×600).