

## REVIEW

## Renal cell carcinomas with a mesenchymal stromal component: what do we know so far?

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## Summary

A subset of renal cell neoplasms contains a mesenchymal stromal component, often resembling smooth muscle. To date, it remains debated whether these represent one or more distinct pathological entities. The foremost of these, renal cell carcinoma with angioleiomyoma-like stroma (also known as smooth muscle or leiomyomatous stroma), has some distinctive features, including immunohistochemical positivity for cytokeratin 7 and often a lack of genetic changes of clear cell renal cell carcinoma. It is debated whether this is related to the much more common clear cell papillary renal cell carcinoma, owing to the substantial similarity of their immunohistochemical phenotypes. The term renal angioadenomatous tumour has been used by some authors in this context, but this is a source of controversy with some believing it is synonymous with clear cell papillary renal cell carcinoma. Smooth muscle-rich renal cancers appear to be enriched in tuberous sclerosis complex patients, but it is likely that these occur sporadically also. Recently, renal cell carcinomas with *TCEB1* mutation and monosomy of chromosome 8 have also been reported. These have been noted to have fibromuscular stroma and cytokeratin 7 reactivity; however, absence of these genetic alterations in renal cell carcinomas with smooth muscle stroma suggests that this represents only one of likely several entities. Other uncommon patterns of renal neoplasms, such as clear cell renal cell carcinoma with degenerative fibrosis or haemangioma-like changes, mixed epithelial and stromal tumour with epithelial proliferation, angiomyolipoma with epithelial cysts, renal cell carcinoma with associated angiomyolipoma, and sarcomatoid renal cell carcinoma may cause diagnostic challenges for the pathologist. Although knowledge of renal cell carcinomas with a stromal component has dramatically increased recently, further study is necessary to understand the molecular pathology of these tumours and if they have implications for inherited tumour syndromes.

**Key words:** Renal cell carcinoma; smooth muscle; renal angioadenomatous tumour; *TCEB1*; angioleiomyoma.

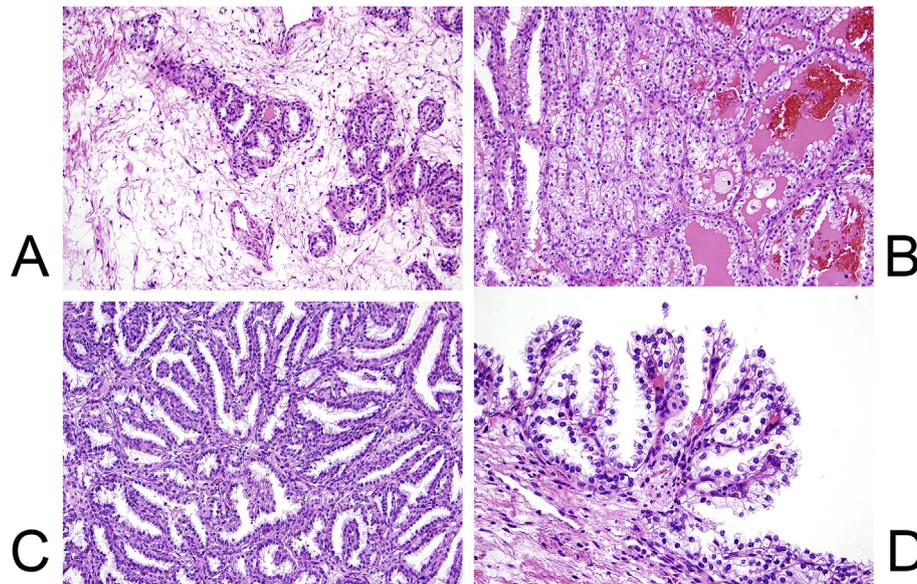
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## INTRODUCTION

Several recent works have described renal tumours that contain renal cell carcinoma admixed with a stromal component, often with a smooth muscle phenotype, imparting the appearance of a biphasic neoplasm.<sup>1–17</sup> These tumours have been described under a variety of names, including renal angioadenomatous tumour,<sup>10</sup> renal cell carcinoma with smooth muscle stroma,<sup>15</sup> renal cell carcinoma with angioleiomyoma-like stroma (or angioleiomyomatous proliferation),<sup>1,5</sup> among others. Additionally, a small body of literature has recently reported tumours with *TCEB1* mutation and monosomy for chromosome 8 that appear to have prominent fibromuscular stroma.<sup>18–20</sup> However, it remains debated and incompletely understood whether these all represent a single diagnostic entity, or whether these reports include multiple pathologically and genetically different entities. Several other biphasic-appearing patterns of renal cell neoplasia have also been described. This review aims to clarify the current state of understanding of these entities.

## CLEAR CELL PAPILLARY RENAL CELL CARCINOMA

Clear cell papillary renal cell carcinoma<sup>21</sup> (also known as clear cell tubulopapillary renal cell carcinoma)<sup>22</sup> is an entity now recognised as a distinct subtype of renal cell carcinoma in the 2016 World Health Organization (WHO) Classification.<sup>21</sup> Despite being only recognised first in 2006 in the setting of end-stage renal disease,<sup>23</sup> it is now known that this is likely the fourth most common renal cell carcinoma subtype (after clear cell, papillary, and chromophobe types), making up 3–4% of adult renal cell carcinomas.<sup>24,25</sup> In fact, most tumours likely occur in non-end-stage kidneys.<sup>24,26,27</sup> Although this tumour typically does not have a stromal component of such a prominent degree that would suggest a biphasic neoplasm or collision of two tumours, it commonly contains loose fibrous stroma (Fig. 1A) intervening between the neoplastic glands that is more conspicuous than that of its close mimic, clear cell renal cell carcinoma.<sup>1,24</sup> Combining this with its debated relationship with the entities renal angioadenomatous tumour and renal cell carcinoma with angioleiomyoma-like stroma, discussed subsequently, it also necessitates discussion in this review.



**Fig. 1** (A) Clear cell papillary renal cell carcinoma can contain prominent stroma, although usually of a loose fibrous quality. (B) Some areas of these tumours can be essentially indistinguishable from conventional clear cell renal cell carcinoma. However, characteristic features include branched glandular structures (C) and small papillary excrescences into cystic spaces (D).

Despite close resemblance of this entity to usual clear cell renal cancer (Fig. 1B), it has a few unique characteristics that facilitate its discrimination by pathologists who are familiar with it. Although some areas may be nearly indistinguishable from clear cell carcinoma morphologically, often other areas contain branched glandular structures (Fig. 1C) or stubby papillary structures (Fig. 1D). The nuclei are often aligned away from the basement membrane (such that the nuclei and cytoplasm resemble the black and white keys of a piano, respectively). Using immunohistochemistry, these tumours have a distinctive profile (Table 1) of positivity for cytokeratin 7, high molecular weight cytokeratin, carbonic anhydrase IX (often cup-shaped), and often GATA3, combined with minimal to negative staining for alpha-methylacyl-CoA racemase (AMACR) and CD10 (sometimes restricted to cysts only).<sup>24,27–30</sup> These tumours almost always lack the classic genetic events of clear cell renal cell carcinoma, particularly chromosome 3p25 loss and *VHL* gene alterations, although a few rare cases have been reported to have these alterations,<sup>31</sup> the significance of which is debatable.<sup>32,33</sup> The importance of this entity is that there remains no example to date with prototypical and well-characterised pathology that has exhibited aggressive behaviour or metastasis, suggesting that this may be reclassified as a benign or low malignant potential tumour in the future.<sup>34,35</sup> Almost all of these are of low-stage (pT1) and low-grade, i.e., WHO/International Society of Urological Pathology (ISUP) grade 1 or 2.

## RENAL ANGIOMYOADENOMATOUS TUMOUR

The entity renal angiomyoadenomatous tumour has been a source of debate.<sup>2,17,36</sup> This tumour type was initially described by Michal *et al.* as a tumour containing leiomyomatous bundles admixed with an adenomatous epithelial component contain clear cytoplasmic ‘snouts’.<sup>9</sup> A series of additional cases was later reported by Michal *et al.*<sup>10</sup> highlighting the distinctive features of this tumour and typical positive immunohistochemical reactivity for cytokeratin 7. Due to the shared features of cytokeratin 7 positivity, branched glandular structures, and areas of nuclear alignment, other authors have asserted that this represents the same entity as clear cell papillary renal cell carcinoma,<sup>2,17</sup> although Michal and colleagues have previously disputed this similarity.<sup>36</sup> The 2016 WHO Classification does not take an entirely definitive stance on this topic, as renal angiomyoadenomatous tumour is listed as a synonym of renal cell carcinoma with angioleiomyoma-like stroma in the table listing provisional/emerging entities, and the text notes that: ‘Some of these tumours are variants of clear cell [renal cell carcinoma] or clear cell papillary [renal cell carcinoma], but there also appears to be a distinct subgroup with characteristic morphological features’.<sup>37</sup> However, at the same time, it also lists renal angiomyoadenomatous tumour as an obsolete synonym in the section on clear cell papillary renal cell

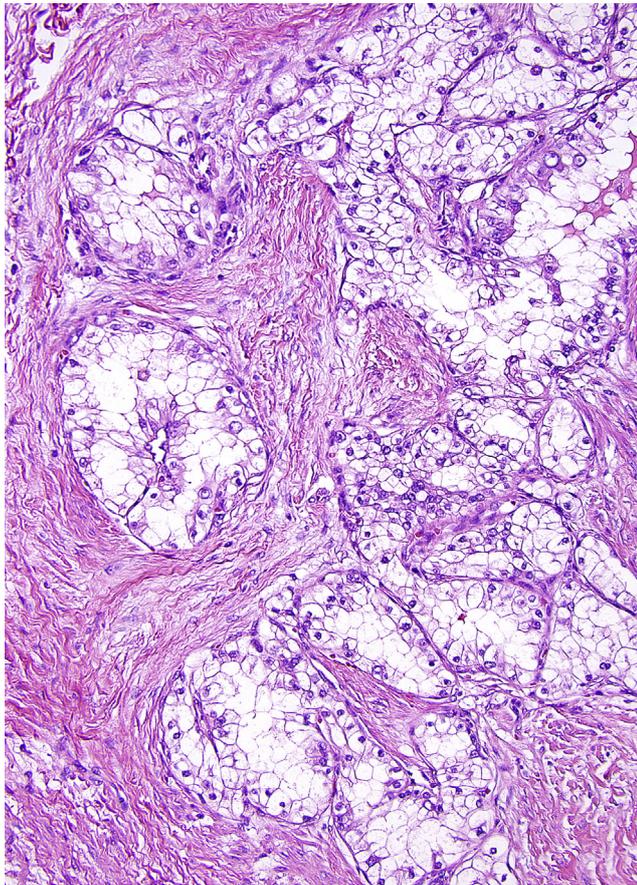
**Table 1** Immunohistochemical features of clear cell papillary (tubulopapillary) renal cell carcinoma

Immunohistochemistry	Features
Cytokeratin 7	Diffuse positive
High molecular weight cytokeratin	Often substantial positivity
Carbonic anhydrase IX	Diffuse positive, often with ‘cup-shaped’ pattern (cell apex negative)
GATA3	Often positive
Alpha-methylacyl-CoA racemase (AMACR)	Negative or minimal
CD10	Negative or focal labelling of cystic areas

carcinoma.<sup>21</sup> In my view, most of the tumours reported under the name renal angiomyoadenomatous tumour would likely qualify for a diagnosis of clear cell papillary renal cell carcinoma (with a predominance of tubular or glandular growth and scant papillary architecture). An exception would be those that show overgrowth of stroma with positivity for smooth muscle markers, often coupled with extension of this muscular component away from the epithelial neoplasm and into perinephric fat or benign kidney. This unique pattern is discussed further under renal cell carcinoma with angioleiomyoma-like stroma. Due to the debate and uncertainty over the term renal angiomyoadenomatous tumour in the literature, my approach is to avoid use of this term, in favour of classifying tumours as either clear cell papillary renal cell carcinoma or renal cell carcinoma with angioleiomyoma-like stroma.

### RENAL CELL CARCINOMA WITH ANGIOLEIOMYOMA-LIKE STROMA

An unusual group of renal cell tumours has been reported to contain leiomyomatous or angioleiomyoma-like stroma that is so prominent as to raise consideration of two admixed neoplasms (Fig. 2).<sup>1,5</sup> In some of these cases, the smooth muscle proliferation also extends away from the renal cell component, to intermingle with perinephric fat or benign renal structures, such as dilated tubules. One might consider whether this represents coexistence of two more common renal neoplasms, clear cell renal cell carcinoma and



**Fig. 2** Renal cell carcinoma with angioleiomyoma-like stroma (also known as smooth muscle or leiomyomatous stroma) typically manifests histologically as glands lined by cells with clear cytoplasm within fibromuscular stroma.

angiomyolipoma; however, this smooth muscle component has been largely found to be negative for melanocytic and other angiomyolipoma markers, such as HMB45, melan-A, and cathepsin K.<sup>1,5</sup> One study (including four renal angiomyoadenomatous tumours/clear cell papillary carcinomas, five clear cell carcinomas, two papillary carcinomas, and three renal cell carcinomas with smooth muscle rich stroma) found that despite the prominence of this leiomyomatous proliferation, it is polyclonal using the human androgen receptor assay for clonality (eight tumours were informative), leading the authors to conclude that this smooth muscle is reactive and not neoplastic.<sup>12</sup> Whereas clear cell renal cell carcinomas typically contain an intricate network of vasculature that invests nearly every nest or glandular structure, these carcinomas with smooth muscle stroma have a variable, sometimes interrupted, layer of capillaries that sometimes cuffs the widely dispersed glandular structures, resembling a basal or myoepithelial cell layer.<sup>1</sup>

This morphology, combined with a unique immunohistochemical phenotype of positivity for carbonic anhydrase IX, high molecular weight cytokeratin, and cytokeratin 7, plus negative staining for AMACR, predominantly appears to correlate with lack of the chromosome 3p loss that is characteristic of clear cell renal cell carcinoma.<sup>1</sup> One study found that of a cohort of three tumours, *VHL* and 3p alterations were lacking using multiple technologies, including fluorescence *in situ* hybridisation (FISH), array comparative genomic hybridisation, gene sequencing, and methylation-specific multiplex ligation-dependent probe amplification analysis.<sup>38</sup> Of note, this phenotype is quite similar to that of clear cell papillary renal cell carcinoma, leading some to speculate that this is part of the spectrum of the same entity. However, a few differences make it less clear whether this is true: (1) renal cell carcinoma with angioleiomyoma-like stroma tends to have prominent staining for CD10 which, although non-specific among renal cell tumours, is consistently minimal or absent in clear cell papillary tumours; (2) it is not clear why there are few appreciable intermediate forms with features in the middle of the spectrum of these two entities (perhaps the tumours considered by some to be renal angiomyoadenomatous tumour might represent this intermediate pattern?); and (3) renal cell carcinoma with angioleiomyoma-like stroma has been found to be enriched in patients with tuberous sclerosis complex,<sup>39,40</sup> yet clear cell papillary tumours do not appear to be particularly common in this context (Table 2). For the most part, tumours with this constellation of features have been found to be non-aggressive, similar to clear cell papillary renal cell carcinomas; however, in the setting of tuberous sclerosis, a few cases with lymph node involvement have been reported.<sup>39,41</sup> This again represents a point of difference with clear cell papillary renal cell carcinomas, for which a much larger number of cases has been studied, and yet none have shown metastases.

Still, despite this unique phenotype of tumours demonstrating smooth muscle stroma, combined with carbonic anhydrase IX +, high molecular weight cytokeratin +, cytokeratin 7 +, CD10 +, AMACR -, and absence of 3p25/*VHL* alterations,<sup>1,42</sup> there are still other tumours that have prominent stroma with some degree of cytokeratin 7 labelling that harbour typical alterations of clear cell renal cell carcinoma, such as *VHL* gene alterations or loss of material from chromosome 3.<sup>1,11,15</sup> As such, it remains to be better defined whether this diagnosis can be made on the basis of

**Table 2** Comparison of features of clear cell papillary renal cell carcinoma and renal cell carcinoma with angioleiomyoma-like stroma (smooth muscle stroma)

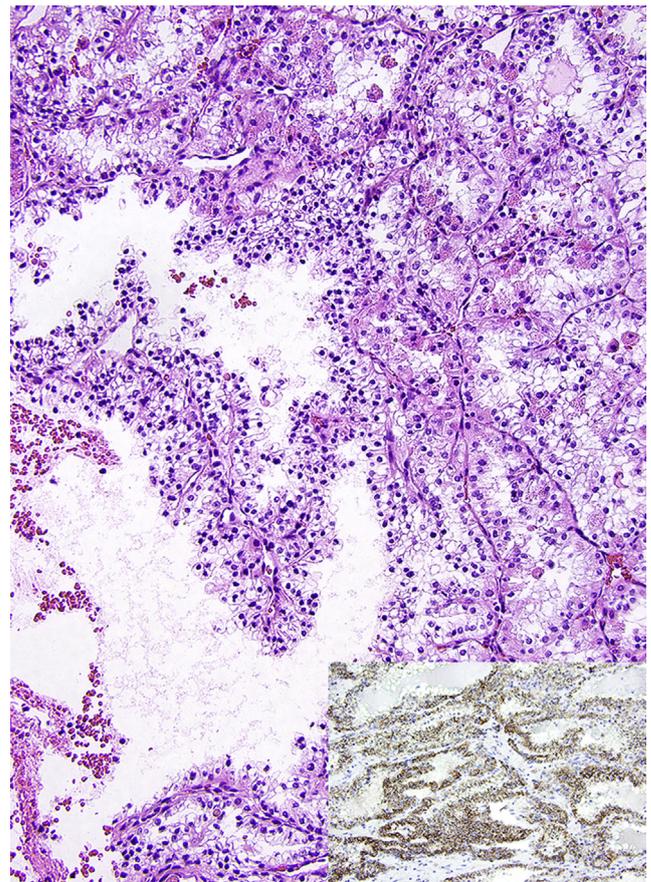
Features	Clear cell papillary	RCC with angioleiomyoma-like stroma
Carbonic anhydrase IX +, cytokeratin 7 +, high molecular weight cytokeratin +	Yes	Yes
Alpha-methylacyl-CoA racemase (AMACR) negative	Yes	Yes
CD10 +	Minimal or cysts only	Yes
Epithelium dispersed in large areas of smooth muscle	No	Yes
Smooth muscle entraps adjacent tissues (fat or non-neoplastic kidney)	No	Yes
SDHB staining weak (sparse mitochondria)	Yes	Yes
3p deletion/ <i>VHL</i> alteration	No	Some with 3p deletion or <i>VHL</i> mutant, of uncertain classification
Aggressive behaviour	None reported from well-characterised cases	Few lymph node involvement in tuberous sclerosis patients
Association with tuberous sclerosis	No	Subset of patients

morphology and immunohistochemistry alone, or whether molecular studies to exclude clear cell renal cell carcinoma genetics are a necessity. Since comprehensively evaluating for alterations of *VHL* is prohibitive for many pathology practices, and since this diagnosis still carries classification as renal cell carcinoma (not benign versus malignant), my approach is to diagnose tumours with this prominent smooth muscle stroma, combined with the expected immunohistochemical phenotype (Table 2), as ‘renal cell carcinoma with angioleiomyoma-like stroma’, with a comment as follows: ‘Renal cell carcinoma with angioleiomyoma-like stroma is a recently recognised neoplasm with mixed epithelial proliferation and smooth muscle-rich stroma that lacks the usual molecular alterations of clear cell renal cell carcinoma. It remains uncertain whether these tumours are related to clear cell papillary renal cell carcinoma (both of which are cytokeratin 7 positive and lack *VHL*/chromosome 3p alterations) or if they should be regarded as a separate distinct tumour type. This morphology appears to be much less common. Two recent studies have found that a similar morphology can be found in patients with tuberous sclerosis complex, although it is not yet known whether this morphology is indicative of tuberous sclerosis or if it also occurs sporadically. To date the behaviour appears mostly non-aggressive, although data are limited.’

### TUMOURS WITH BORDERLINE FEATURES

For tumours that have an imperfect immunohistochemical staining pattern for either clear cell papillary renal cell carcinoma or renal cell carcinoma with angioleiomyoma-like stroma, it appears that the best approach is to regard them as clear cell renal cell carcinomas. This comes from a few studies that have found that imperfect morphological features or immunohistochemistry results often correlate with genetic alterations of clear cell renal cell carcinoma and/or more aggressive behaviour than that of clear cell papillary carcinomas.<sup>6,13,43,44</sup> For example, in a study by Petersson *et al.* of tumours with partial morphology of clear cell papillary renal cell carcinoma/renal angioleiomyomatous tumour, five of seven had alterations of *VHL*.<sup>13</sup> In another study from our group, 68% of tumours with partial features suggestive of clear cell papillary renal cell carcinoma had chromosome 3p loss as detected by FISH, of which most had an imperfect immunohistochemical staining pattern, often with greater than acceptable amounts of positivity for CD10 or AMACR (Fig. 3).<sup>44</sup> Likewise, Dhakal *et al.* found that a substantial

number of cases with features overlapping between clear cell renal cell carcinoma and clear cell papillary renal cell carcinoma exhibited higher grade or stage, some showing distant metastases, supporting the classification of these as clear cell renal cell carcinomas.<sup>43</sup> In contrast, the vast majority of well-characterised cases of clear cell papillary renal cell carcinoma have been of low-grade (ISUP/WHO grade 1 or 2), with perhaps rare exception reaching grade 3.<sup>24</sup> The tumours with angioleiomyoma-like stroma, of note, seem to have a



**Fig. 3** Some clear cell renal cell carcinomas can have borderline features of clear cell papillary tumours (or smooth muscle rich tumours). This example has substantial labelling for alpha-methylacyl-CoA racemase immunohistochemistry (inset), arguing against inclusion in one of these categories and supporting classification as clear cell renal cell carcinoma. The same tumour had substantial but incomplete positivity for cytokeratin 7 and negative results for high molecular weight cytokeratin and GATA3 (not pictured).

tendency to be grade 2 or occasionally grade 3.<sup>1</sup> Some studies have found that it can be difficult to distinguish renal cell carcinomas with leiomyomatous stroma that are negative for *VHL* alterations from those that harbour alterations.<sup>11</sup> Overall, my approach is to evaluate a tumour with borderline or imperfect features using immunohistochemistry, especially if there are worrisome findings, such as higher stage, higher grade, or necrosis. In most cases, the immunohistochemical phenotype does not fit with the expected results of these entities,<sup>44</sup> in which case, it is likely best to classify the tumour as a clear cell renal cell carcinoma.

## DIFFERENTIAL DIAGNOSIS OF RENAL CELL CARCINOMA WITH SMOOTH MUSCLE STROMA

### Sarcomatoid renal cell carcinoma

Sarcomatoid renal cell carcinoma might be a consideration when evaluating a neoplasm with mixed epithelial and stromal components. The mesenchymal component of sarcomatoid renal cell carcinoma is typically evident as malignant histologically, usually being of intermediate to high grade; however, a subset cases include a relatively low-grade sarcomatous component,<sup>45,46</sup> such that distinction from a stromal component could be a challenge (Fig. 4). The mesenchymal component of sarcomatoid renal cell carcinoma typically retains some evidence of epithelial differentiation via immunohistochemical markers, such as positivity for PAX8 or keratins.<sup>47,48</sup> Additionally, the mesenchymal component is typically negative for desmin, arguing against smooth muscle differentiation,<sup>49</sup> in contrast to renal cell neoplasms with a stromal component.

### Mixed epithelial and stromal tumour with epithelial neoplasia

Mixed epithelial and stromal tumour of the kidney is a biphasic neoplasm that typically contains a mesenchymal, spindle-shaped cell component (variably hypocellular and fibrous or cellular), as well as an epithelial component, ranging from crowded, branching glands, to clusters of cuboidal-lined glands, to broad papillae resembling phyllodes tumour. Often, the stroma is referred to as resembling ovarian stroma, at least partially.<sup>50–54</sup> Usually, mixed epithelial and stromal tumour would not be considered in the differential diagnosis of a renal cell carcinoma with a stromal proliferation; however, rare cases have been reported in which the epithelial component is proliferative, to the point that it is considered a renal cell carcinoma.<sup>55</sup> A metanephric adenoma arising in a mixed epithelial and stromal tumour has also been reported.<sup>56</sup> Such situations appear to be quite rare, however, with most examples of putative ‘malignant’ mixed epithelial and stromal tumours instead representing sarcomatous transformation.<sup>57–61</sup> The stromal component of mixed epithelial and stromal tumour characteristically is positive for oestrogen or progesterone receptors and is frequently positive for smooth muscle markers, such as smooth muscle actin, desmin, or caldesmon.<sup>50–54</sup> Although relatively few renal cell carcinomas with smooth muscle stroma have been studied for oestrogen and progesterone receptors, several cases have shown negative or focal labelling, as a point of contrast.<sup>1</sup> One very unique histology that has been recently described as smooth muscle and adenoma-like renal tumour (or

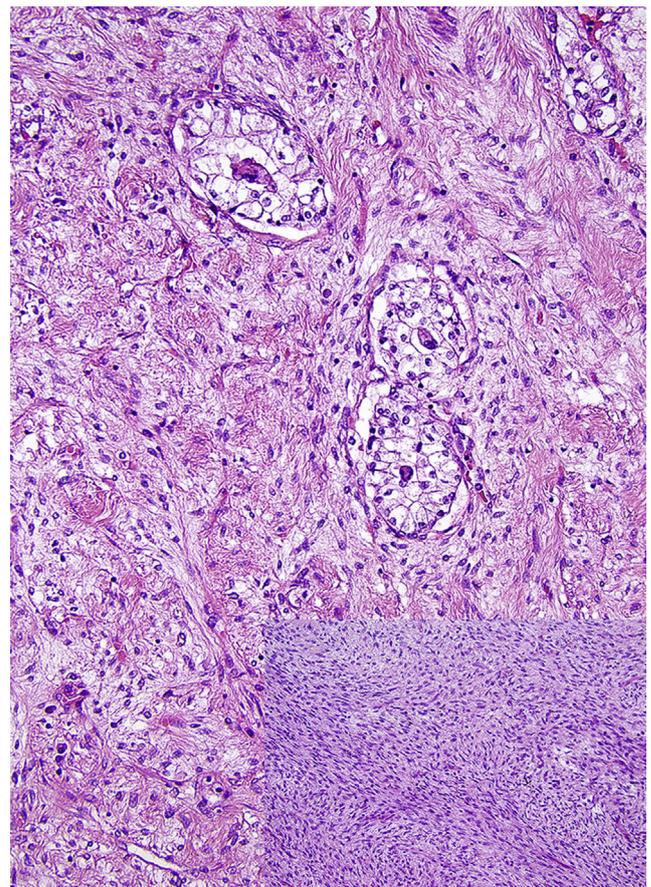
SMART),<sup>62</sup> could be debated as a variant of mixed epithelial and stromal tumour or its own distinctive subtype of neoplasm. This is discussed later.

### Concomitant renal cell carcinoma and angiomyolipoma

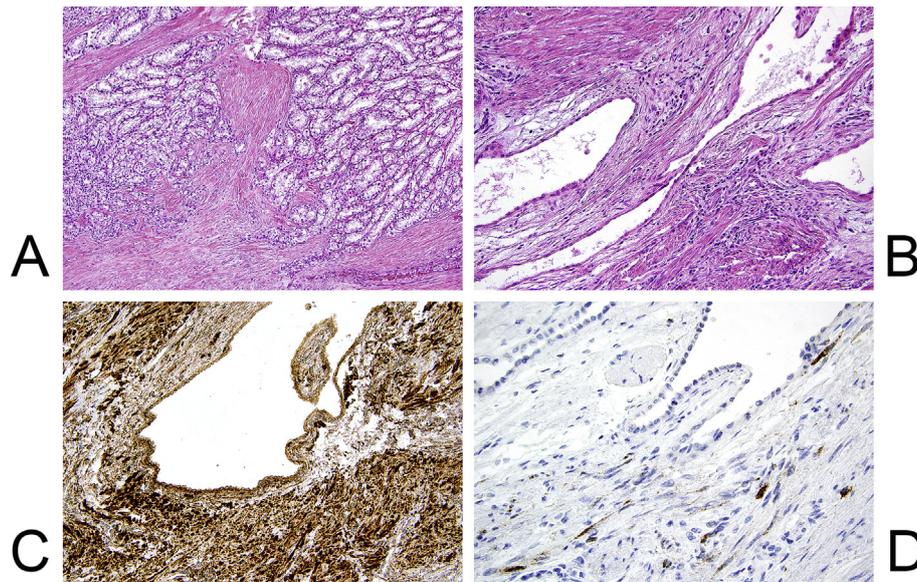
One of the first hypotheses explored for renal cell carcinoma with smooth muscle stroma was that it might represent a collision tumour between angiomyolipoma and renal cell carcinoma; however, this was argued against even in the first study by negative staining for HMB45 and melan-A.<sup>5</sup> Other studies have found similarly, additionally showing negative cathepsin K staining,<sup>1</sup> indicating that the stroma is not entrapped angiomyolipoma. However, the occurrence of angiomyolipoma in intimate association with renal cell carcinoma is possible, especially in the setting of tuberous sclerosis, in which angiomyolipomas may be numerous (Fig. 5).<sup>63,64</sup>

### Angiomyolipoma with epithelial cysts

Angiomyolipoma has been long-recognised as a benign renal neoplasm, composed of spindle-shaped myoid cells, lipid-laden cells resembling fat, and blood vessels with thick walls. However, recent attention has been drawn to an uncommon variant, termed angiomyolipoma with epithelial cysts (or AMLEC), which contains cystic renal tubules with a



**Fig. 4** Sarcomatoid renal cell carcinoma can occasionally have a deceptively bland mesenchymal component. This case was originally misdiagnosed as a renal cell carcinoma with a stromal component. However, on closer inspection, some areas have a fibrosarcoma-like mesenchymal appearance (inset) favouring sarcomatoid renal cell carcinoma. This patient developed metastasis to the orbit after resection of the renal tumour.



**Fig. 5** (A) Renal cell carcinoma with angioleiomyoma-like stroma may be enriched in patients with tuberous sclerosis complex. This patient met clinical criteria for tuberous sclerosis and had numerous angiomyolipomas and renal cell carcinomas. (B) Incidental microscopic angiomyolipoma was closely associated with the renal cell carcinoma and contained a few cystic benign tubules. (C) Immunohistochemistry demonstrates strong labelling for cathepsin K in the same area and (D) focal labelling for HMB45.

benign histological appearance.<sup>65–68</sup> Similar to mixed epithelial and stromal tumour, this would typically not be confused with a renal cell carcinoma containing a stromal proliferation, at least after the histopathology is examined. For example, renal cell carcinoma was not in the pathological original diagnoses of 11 cases reported by Davis *et al.*<sup>68</sup> To my knowledge, no example of proliferative epithelium resembling a renal cell carcinoma has been noted in this context, although it is difficult to exclude that some of the concurrent angiomyolipomas and renal cell carcinomas that have been reported could have arisen this way. Current thinking is the cystic component represents entrapment of benign renal tubules, in view of positivity for PAX8 or PAX2 and absence of positivity for melanocytic markers.<sup>66</sup>

### ASSOCIATION WITH TUBEROUS SCLEROSIS COMPLEX

Two major studies nearly simultaneously investigated the spectrum of renal cell carcinoma in tuberous sclerosis patients.<sup>39,40</sup> In the series by Yang *et al.*, 24 tumours were referred to as tuberous sclerosis complex-associated papillary renal cell carcinomas.<sup>40</sup> Although these appeared to have predominantly papillary architecture, in contrast to other reports of renal cell carcinoma with angioleiomyoma-like stroma,<sup>1</sup> at least some of the areas illustrated showed a more solid appearance with fibromuscular stroma, and the reported immunohistochemical phenotype was essentially identical to that of the renal cell carcinomas with smooth muscle stroma (Fig. 5).<sup>40</sup>

Interestingly, Yang *et al.* noted abnormal negative staining of these tumours for succinate dehydrogenase B,<sup>40</sup> which is unexpected, since succinate dehydrogenase genetic alterations are thought to be characteristic of succinate dehydrogenase-deficient renal cell carcinoma and the pheochromocytoma-paraganglioma syndromes caused by germline mutations, whereas tuberous sclerosis complex is associated with alterations in the *TSC1* and *TSC2* genes that

encode hamartin and tuberin, respectively. A recent study from our group found that both clear cell papillary renal cell carcinoma and the tumours with smooth muscle stroma seem to have minimal staining for succinate dehydrogenase B, perhaps reflecting the scarcity of mitochondria within the cells.<sup>69</sup> This is also supported by another abstract, which found that clear cell papillary renal cell carcinoma has depletion of mitochondrial content.<sup>70</sup> Therefore, it seems likely that the negative staining result identified by Yang *et al.*<sup>40</sup> may be a false-negative result, due to the scant positivity in the cells of these tumours.

In the series by Guo *et al.*,<sup>39</sup> similarly 17 renal cell carcinomas (30% of tuberous sclerosis-associated cases) had morphology similar to that of renal angiomyoadenomatous tumour/renal cell carcinoma with smooth muscle stroma, including one which metastasised to a lymph node.<sup>39</sup> Following these two studies that demonstrate enrichment of this histology in the setting of tuberous sclerosis, a logical question would be to consider whether finding this histology in an apparently sporadic renal tumour suggests undiagnosed or *forme fruste* of tuberous sclerosis. In the series from our group, there was no convincing evidence of tuberous sclerosis stigmata in a series of apparently sporadic tumours;<sup>69</sup> however, a French group in an abstract found the contrary, with 35% of patients appearing to have signs of tuberous sclerosis.<sup>41</sup> Likewise, a recent case report found an atypical manifestation of tuberous sclerosis presenting with multiple renal cell carcinomas with angioleiomyoma-like stroma.<sup>71</sup> Therefore, a potentially reasonable working hypothesis is that this tumour can occur both in the setting of tuberous sclerosis and sporadically, although more study is needed. Overall, there is rapidly expanding understanding of the role of the tuberous sclerosis genes in renal neoplasia, with alterations in *TSC1*, *TSC2*, and *MTOR* found in recently characterised subtypes of renal neoplasms that appear to be at least partly sporadic, including eosinophilic solid and cystic renal cell carcinoma and high-grade oncocyctic tumour.<sup>72–76</sup>

### CLEAR CELL RENAL CELL CARCINOMA WITH ENTRAPPED MUSCLE

Occasionally clear cell renal cell carcinoma can have entrapped muscle, which seems to generally correlate with invasion of structures, such as the renal sinus or perinephric tissue.<sup>1</sup> In such cases, the immunohistochemical phenotype is largely that of a typical clear cell renal cell carcinoma, with limited cytokeratin 7 positivity, limited or negative high molecular weight cytokeratin reactivity, and some degree of immunohistochemical positivity for CD10 or AMACR.<sup>1</sup> Similarly, tangential sectioning of the tumour pseudocapsule can occasionally impart an appearance resembling smooth muscle stroma, but this typically is present only in a single tissue block of a tumour otherwise resembling typical clear cell renal cell carcinoma.<sup>1</sup>

### CLEAR CELL RENAL CELL CARCINOMA WITH STROMAL SCLEROSIS OR HAEMANGIOMA-LIKE CHANGES

It is relatively common for clear cell renal cell carcinoma tumours to include areas of fibrosis or scarring. Usually, this poses no diagnostic challenge; however, rare cases have been described in which the extent of scar or regressive change is so extensive that the epithelial component of the tumour is almost obscured, mimicking haemangioma (Fig. 6).<sup>77-79</sup> For the most part, such tumours have straightforward features of clear cell renal cell carcinoma partially within the neoplasm, facilitating the diagnosis. However, it is noteworthy that multiple keratin or renal epithelial immunohistochemical markers may be necessary to identify the epithelial component of challenging cases, as clear cell renal cell carcinoma can have variable positivity for general cytokeratins, such as keratin AE1/AE3 or CAM 5.2.<sup>79</sup> PAX8 and carbonic anhydrase IX are generally robust markers to identify the clear cell epithelial cells in such tumours, which can be confused with lymphocytes or capillaries.<sup>79,80</sup>

### TCEB1 MUTATED RENAL CELL CARCINOMA

Renal cell carcinoma with *TCEB1* mutation (Fig. 7) is an emerging subcategory of renal cancer that is incompletely understood to date. One major study identified 11 cases from two major genomic profiling cohorts of clear cell renal cell carcinoma, finding this genetic alteration to be mutually exclusive with abnormalities of *VHL*.<sup>18</sup> Hakimi *et al.* noted that these tumours had positivity for cytokeratin 7 immunohistochemistry and prominent fibromuscular bands. Data presented in another abstract also suggests that these tumours typically have monosomy of chromosome 8 (where the *TCEB1* gene resides).<sup>19</sup> A series by Lan *et al.* found two tumours from a cohort of six with unclassified tubulopapillary pattern to have monosomy of chromosome 8 in conjunction with cytokeratin 7 positivity.<sup>20</sup> Although sequencing of *TCEB1* was not included in the study, the tumours were later found to be *TCEB1* mutated (personal correspondence, Dr Tatjana Antic, University of Chicago). Similarly, a recent series from Pei *et al.* found three tumours from a cohort of 14 with low-grade clear cell and papillary features to have monosomy 8 (again without sequencing of *TCEB1*).<sup>81</sup> Although it would be tempting to assume that this molecular alteration may be the missing link that explains all of the previously reported renal cell carcinomas with smooth

muscle stroma, a handful of recent studies and abstracts have found that *TCEB1* mutations or monosomy 8 are lacking from renal cell tumours with smooth muscle stroma,<sup>42,82,83</sup> suggesting that these still represent two separate, small subsets of renal neoplasms.

### SMOOTH MUSCLE AND ADENOMA-LIKE RENAL TUMOUR

To date, only one series has reported a unique renal tumour histology composed of smooth muscle-rich stroma and tubulopapillary proliferative epithelium resembling papillary renal cell carcinoma or papillary adenoma.<sup>62</sup> This series used the nomenclature smooth muscle and adenoma-like renal tumour (SMART). Although the authors acknowledged the possibility that some might consider this to be a variant of mixed epithelial and stromal tumour, several differences were noted, including predominance of smooth muscle stroma (with absence of ovarian-like or fibrotic stroma) and typical negative results for oestrogen receptor immunohistochemistry.<sup>62</sup> The stroma of these tumours was found to be positive for desmin, whereas the epithelium was noted to have a pattern reminiscent of papillary renal cell carcinoma, including positivity for cytokeratin 7, PAX8, and patchy AMACR, with negative carbonic anhydrase IX. Despite the resemblance to papillary renal cell carcinoma, none of the

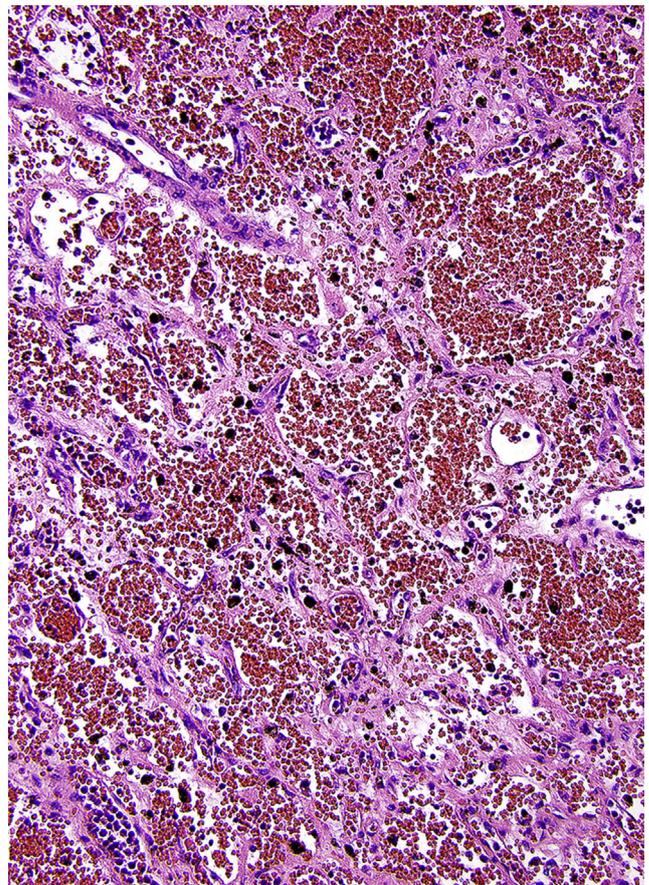
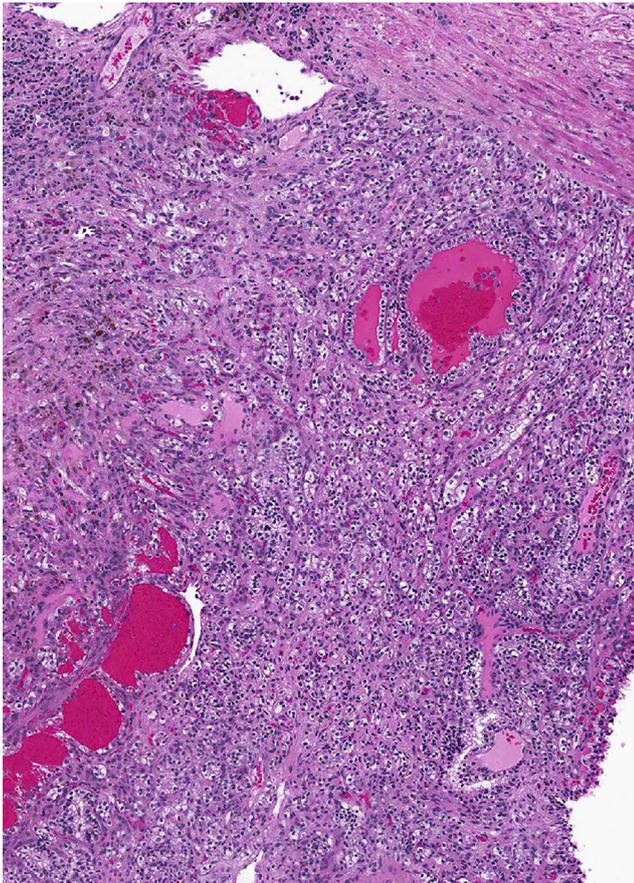


Fig. 6 Occasionally, clear cell renal cell carcinoma can contain degenerative changes that mimic haemangioma. This example has inconspicuous epithelial cell lining of the haemorrhagic spaces, which could be mistaken for haemangioma if encountered in a biopsy sample.



**Fig. 7** *TCEB1* mutant renal cell carcinoma is an emerging category of renal neoplasia that may be difficult to discriminate based only on morphology. This example from the Cancer Genome Atlas database (<https://portal.gdc.cancer.gov/>) closely resembles a clear cell renal cell carcinoma, with minimal fibromuscular stroma.

five cases tested by fluorescence *in situ* hybridisation had trisomy 7 or 17.<sup>62</sup>

## OTHER HISTOLOGIES WITH SMOOTH MUSCLE STROMA

Although most of the published cases containing exuberant stroma have had an epithelial component resembling clear cell (or clear cell papillary) renal cell carcinoma, a few examples of other histologies have been described, particularly papillary renal cell carcinoma.<sup>12</sup> Due to the rarity of this occurrence, it is not clear what the significance of this finding is, if any. In one of the published examples,<sup>12</sup> the illustration of this phenomenon in a papillary renal cell carcinoma is focal, in which case, it may represent a reactive phenomenon from invasion or entrapment of structures, similar to what has been found for some clear cell cancers.<sup>1</sup>

## CONCLUSION

In summary, knowledge of renal cell neoplasms with a stromal component (often having a smooth muscle phenotype) has dramatically increased recently. However, several aspects of the understanding of these neoplasms requires further study, in particular whether there are one or more distinct pathological entities, the genetics of such tumours, and whether identification of such neoplasms has any

implication for diagnosis of hereditary syndromes, particularly tuberous sclerosis.

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