# Pleomorphic adenoma with PLAG1 fusion as an isolated kidney mass: lessons learned from a challenging case

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# Lesson of the Month

## Pleomorphic adenoma with *PLAG1* fusion as an isolated kidney mass: lessons learned from a challenging case

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Metastasising pleomorphic adenoma (PA) of the salivary glands is an infrequent diagnosis, with 81 cases described from 1942 to 2015.[1] Histopathologically, it is indistinguishable from regular PA. The time from diagnosis of primary tumour to metastasis is widely variable, from 0 to 51 years. Most cases are identified in the bone. The majority of patients are alive at 1 year, but 17.6% died from disease.[1,2] Cytogenetic abnormalities are identified in approximately 70% of PA and 25% involve the 8q12 region, which includes *PLAG1*. This is frequently found in fusions, both in primary tumours and in metastasising PA.[3]

We report the case of a 43-year-old female patient presenting with a history of vague lumbar pain for years. Imaging identified a large mass in the inferior pole of the left kidney. A primary renal cell carcinoma (RCC) was suspected and partial nephrectomy was performed. The surgical specimen was almost completely occupied by a well-demarcated whitish-beige tumour mass, measuring 80 × 70 × 70 mm (Figure 1A). Histologically, it showed a solid, multinodular growth pattern with pushing borders. It had a triphasic appearance, composed of two populations of cells (epithelial and myoepithelial) and stroma (Figure 1). There were areas with tubular/glandular structures, strongly positive for CK7, CK19 and for pan-cytokeratins (Figure 2), and surrounding smaller, basaloid and spindle myoepithelial cells, strongly positive for S100, GFAP, SMA, calponin and p63, but weakly positive for pan-cytokeratins. Tumour cells

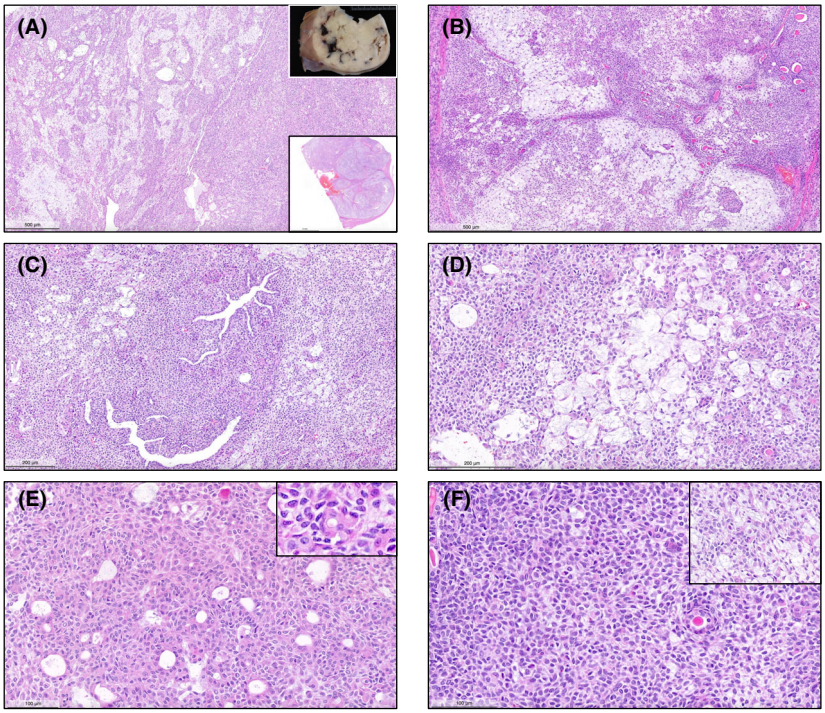


**Figure 1.** Histopathological features of the renal tumour. The tumour was grossly well-demarcated and unencapsulated. The cut surface was whitish-beige solid, vaguely lobulated, with few small cystic areas. There were minor foci of haemorrhage, and no necrosis was evident. The tumour was limited to the kidney (**A**, top inset). Histologically it had a lobulated appearance, pushing the renal parenchyma (**A**, bottom inset). There were areas with more solid growth and others with intervening stroma (**A**). The tumour was heterogeneous, with obvious tubule formation, sometimes with eosinophilic secretion, and with oedematous and mucinous/myxoid stroma (**B**). Tubular structures were sometimes elongated, slit-like, and surrounded by a second population of basaloid cells with scant cytoplasm (**C**). Tubules were lined by eosinophilic cuboidal cells with round nuclei and small nucleoli. At the periphery of the tubules and intermingling with the myxoid stroma there was a population of more flattened or spindled cells, with pale cytoplasm. Some of these had a stellate or plasmacytoid appearance (**D**, **E**, inset). While in some areas tubular formation was abundant (**E**), in others the pale cells were dominant (**F**). There were foci with evident plasmacytoid and spindled features (**F**, inset).

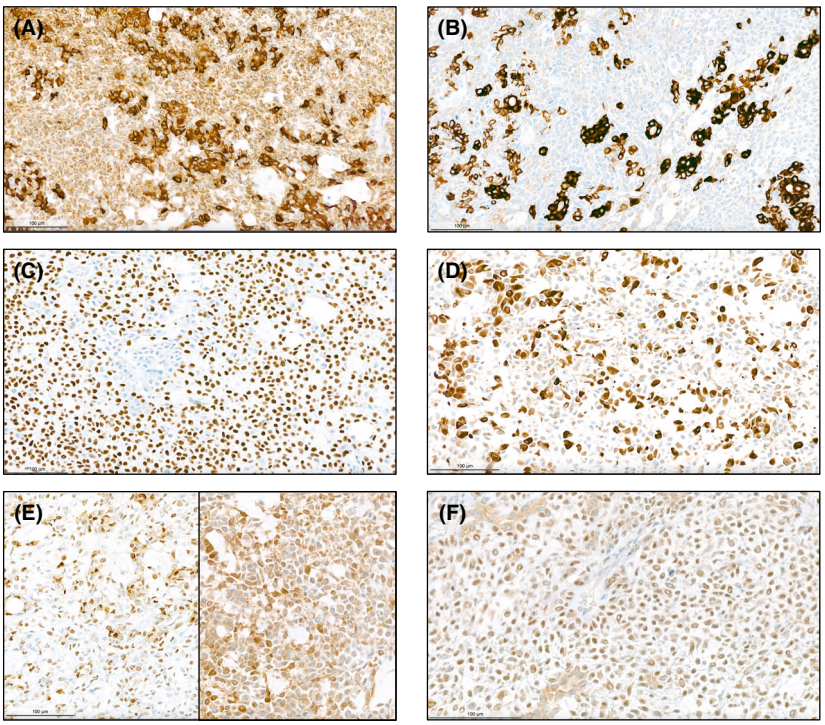


**Figure 2.** Immunohistochemistry studies. The tumour was positive for pan-cytokeratins, more strongly in the tubular structures and weakly in the myoepithelial cells (**A**). The tubular structures were strongly positive for CK7 (**B**). The myoepithelial cell population was diffusely positive for p63 (**C**), GFAP (**D**), S100 (**E,** left) and calponin (**E,** right). The tumour showed diffuse nuclear immunoexpression of PLAG1 (**F**).

merged intimately with the stroma, which was myxoid/mucinous and oedematous, creating a lacelike pattern. There were no mitoses or necrosis. FH, SDHB and INI1 expression were retained. Immunohistochemistry for PAX8, EMA, WT1, ALK, desmin, ER, PR, inhibin, TTF-1, CK20, TGB, CD34, CD117, CD56 and synaptophysin was negative. Proliferative index (Ki67) was low (< 5%). Tumour cells showed diffuse nuclear positivity for PLAG1. Fluorescence *in situ* hybridisation for *ALK* alterations was negative and no *SS18* rearrangements were found. This immunophenotype was unusual for a primary RCC subtype, and triggered a next-generation sequencing (NGS) analysis. NGS detected *CTNNB1*::*PLAG1* (split read 60.21%) and *CHCHD7*::*PLAG1* (split read 18.48%) fusion, suggestive for a PA in the kidney. A diagnosis of PA was unknown to the clinicians, but on referring back to the patient, she revealed that she had removed a salivary gland tumour with 12 years of age, 31 years before partial nephrectomy. Pathological report confirmed diagnosis of PA in the salivary gland, but histological slides and paraffin blocks were unavailable after this very long time.

The patient is disease-free at 24 months after kidney surgery. There are reports of 'benign mixed renal tumours', which were later confirmed to represent metastases from an unrecognised primary salivary gland tumour.[4] The time from primary salivary gland tumour excision to presentation with a single renal mass can be considerable (31 years in our case, the longest reported so far).[1]

Recently, Parwani *et al.*[5] and Pacchioni *et al.*[6] reported a set of renal tumours with some specific features reminiscent of PA and designated them as 'low-grade myxoid renal epithelial neoplasms' or 'myxoid renal tumour with evidence of myoepithelial differentiation'. A distal nephron origin was suggested, but considered very hypothetical. Myoepithelial differentiation is hard to explain in the kidney, as it is restricted to the Bowman's capsule. In their case, no primary salivary gland tumour was diagnosed with 3 years follow-up, but molecular studies, including *PLAG1* testing, were not performed. It is tempting to speculate that most (if not all) of these reported tumours are indeed salivary gland tumours.

In our case, a further molecular differential diagnosis included myoepithelial carcinoma of the salivary gland (*de-novo*) or ex-PA, also potentially harbouring *PLAG1* gene fusions. These were discarded due to the mixed differentiation and the lack of invasion/infiltration. Metastasising PA is proposed to arise from embolism of benign tumour cells displaced during

 

surgical resection, supported by a higher incidence after laborious/incomplete resections.[1] While malignant salivary gland tumours such as adenoid cystic carcinoma may metastasise to the kidney, only eight cases of metastasising PA involving the kidney were reported until 2018.[1] Presentation as a single incidental kidney mass is unusual, and creates several challenges in differential diagnosis with various primary renal tumour entities, including mucinous tubular and spindle cell carcinoma, tumours of the mixed epithelial and stromal tumour family, metanephric adenoma, biphasic synovial sarcoma or *ALK* translocated renal cell carcinoma. These diagnoses were excluded after immunohistochemistry/molecular studies. Evidence of a myoepithelial cell population was also not supportive of any of these diagnoses. Identification of *PLAG1* fusion by NGS and diffuse PLAG1 expression rendered our diagnosis of PA in the kidney. This prompted us to request a more detailed patient interview, which revealed history of a submandibular gland PA.

Our case highlights the need to exclude a salivary gland tumour in the presence of tumours with myoepithelial differentiation, the need to obtain a complete medical history of the patient and to maintain close follow-up for several years.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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## Ethics

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**File S1.** Materials and methods.

**Table S1.** Details about immunohistochemistry studies.