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ORIGINAL ARTICLE

Immunohistochemical distinction of metastases of renal cell carcinoma to the adrenal from primary adrenal nodules, including oncocytic tumor

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Abstract Metastases of clear cell renal cell carcinoma to the adrenal can mimic primary adrenal cortical neoplasms or normal adrenal, especially in biopsy material. We compared 34 cases of clear cell renal cell carcinoma metastasis to the adrenal with 49 primary adrenal lesions (16 carcinoma, 22 adenoma, 9 oncocytic tumor, and 2 hyperplasia). Normal adrenal was available in 59 cases. Each entity was represented on tissue microarrays by duplicate-triplicate evaluable spots taken from spatially separate areas. Two pathologists evaluated all reactivity from 0 to 3+. A panel of 12 immunohistochemical stains was performed, including the first diagnostic uses of steroid receptor coactivator (SRC1) and equilibrative nucleoside transporter 1 (ENT1). The most sensitive and specific renal cell carcinoma markers were membranous reactivity for carbonic anhydrase IX (CAIX) and RCC marker and nuclear reactivity for PAX8. For adrenal cortical carcinomas, best markers were synaptophysin, SRC1, and MelanA; and for adrenal oncocytic tumor, synaptophysin and ENT1. Optimal markers for adrenal cortical adenoma and normal adrenal were ENT1 (more specific) and either MelanA or SRC1 (more sensitive). Calretinin, cytokeratin 34βE12 and CAM5.2, inhibin, and steroidogenic factor 1 (SF1) proved less valuable to the panel. Nonspecific cytoplasmic biotin reactivity was frequent for CAIX and PAX8. Tumors with high-grade cytology should be worked up with 2 of the 3 stains: CAIX, PAX8, or RCC marker; and either SRC1 or MelanA. Adrenal adenoma, or normal adrenal, versus low-grade renal cell carcinoma are distinguished by a panel of: CAIX, PAX8, or RCC Marker; ENT1 and either SRC1 or MelanA.

Keywords Adrenal · Adenoma · Carcinoma · Oncocytic tumor · Metastasis · Renal cell carcinoma

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Introduction

The morphology of low-grade clear cell renal cell carcinoma overlaps with normal adrenal and that of high-grade clear cell carcinoma overlaps with primary adrenal adenoma and carcinoma. This can lead to diagnostic dilemmas, particularly in the rare instance of an unknown or remote renal cell carcinoma. History of a known renal cell carcinoma should be sought when possible. If adrenalectomy accompanies nephrectomy, a known concomitant renal cell carcinoma usually is enough to establish the diagnosis of metastasis to the adrenal. Histologic findings may be available, such as bubbly cytoplasm, which favors primary adrenal cortical lesions, or blood lakes which favor renal cell carcinoma. However, biopsies that sample small amounts of adrenal tissue or adrenalectomy performed without nephrectomy can result in diagnostically challenging lesions.

Although prior papers have delineated certain antibodies that are reactive in primary adrenal lesions, most of them did not make a comparison with metastatic renal cell carcinoma [1–3], tested only a single antibody [4–6], or dealt with the differential diagnosis of renal and adrenal tumors in metastatic locations other than the adrenal [7]. One study compared panels of antibodies for primary adrenal lesions versus metastatic renal cell carcinomas of

which five were in the adrenal [8]. Our study is the first to address the predictive value of using combinations of proposed immunostains for the diagnoses in question. A second novel aspect of our study is the first testing of the discriminatory value of new endocrine markers such as ENT1, SRC1, and SF1 (Table 1), not previously been tested in this context. A third novel aspect is the first determination of the immunohistochemical profile of nine cases of oncocytic tumor, which represents 11 % of adrenal tumors [9]. In this study, we applied a panel of 12 antibodies—the most comprehensive studied to date—to 83 cases of adrenal lesions and to accompanying normal adrenal to establish the antibodies' ability, alone or in combination, to discriminate these lesions in the most cost-effective manner.

Materials and methods

Patients and tissues

A search for adrenal lesions was conducted among the surgical pathology files in the departments of pathology at Medical College of Wisconsin (29 cases), Charles University Hospital, Plzen, Czech Republic (36 cases), and Case Western Reserve University (18 cases) during the years 1996–2014.

Slides were reviewed to validate the original diagnoses, namely, 34 clear cell carcinomas (and 3 papillary renal cell carcinomas) metastatic to the adrenal, 16 primary adrenal cortical carcinomas, 22 adrenal cortical adenomas, 9 adrenal cortical oncocytic tumors, and 2 cases of adrenal hyperplasia. Evaluable normal adrenal tissue was available from 59 of the same 83 cases. Clinical information and demographics were abstracted from the patients' charts.

Immunohistochemistry

The hematoxylin-eosin stained glass slides were reviewed on each case, and representative paraffin-embedded blocks were available for immunohistochemical studies on all cases. Triplicate, *spatially separate* areas of both tumor and normal adrenal were punched from paraffin blocks and assembled into three tissue microarrays. At least two evaluable spots were required for each entity. Immunostains were done using the antibodies whose vendors and reaction conditions are listed in Table 1. Strength of immunoreactivity was rated from 0 to 3+ by two pathologists (HL, KI).

Statistical analysis

Logistic regression with generalized estimating equations (GEE) was performed, and a complete sensitivity/specificity report was generated. Sensitivity and specificity were based on the ability to rule in or rule out an adrenal lesion or normal adrenal vs. renal cell carcinoma. Decision rules were determined according to the area under the curve at the 1+, 2+, and 3+ cut points of staining reactivity; all results presented are

Table 1 Immunostains used

Antigen	Clone	Animal	Dilution	Retrieval	Source
Calretinin	DAK-Calret 1	MM	RTU	Tris	Dako (Carpinteria, CA)
CAIX	H-120	RP	1:50	HIER/Tris pH 9.0	Santa Cruz Biotech (Santa Cruz, CA)
CK7/8	CAM5.2	MM	RTU	Citrate	BD Biosciences (Franklin Lakes, NJ)
High MW CK	34βE12	MM	1:150	HIER/Tris pH 9.0	Dako
ENT1[c]	HPA012383	RP	1:100	HIER/Tris pH 9.0	Sigma Aldrich (St. Louis, MO)
Inhibin α	R1	MM	RTU	Tris	Dako[b]
MelanA (MART-1)	A103	MM	RTU	Tris	Dako
Paired box 8 (PAX8)	10336-1	RP	1:100	Tris	Proteintech Group (Chicago, IL)
RCC marker	SPM314	MM	RTU	Citrate	Dako
SF1	E18	GP	1:100	HIER/Tris pH 9.0	Santa Cruz Biotech
SRC1[a, c]	128E7 rabbit monoclonal	RM	1:100	Tris	Cell Signaling (Danvers, MA)
Synaptophysin	DAK-SYNAP	MM	RTU	Tris	Dako

EIER enzyme-induced epitope retrieval with proteinase K, Dako; *GP* goat polyclonal, *HIER* heat-induced epitope retrieval, *MM* mouse monoclonal, *RM* rabbit monoclonal, *PR* rabbit polyclonal, *RTU* ready to use

[a] Steroid receptor coactivator 1

[b] Mouse linker from Dako used after primary antibody to enhance staining

[c] Positive control was Leydig cell tumor of testis

Table 2 Clinical and demographic data

Diagnosis	Men	Women	Age range
Metastatic renal cell carcinoma, clear cell	24	10	41–84
Metastatic renal cell carcinoma, papillary	1	2	73–76
Adrenal hyperplasia	1	1	58, 61
Adrenal cortical adenoma	7	7	41–69
Oncocytic adrenocortical tumor	3	6	29–64
Adrenal cortical carcinoma	9	13	24–71

based on a 2+ cut point, judged to be reproducibly robust [8]. Combinatorial analysis of antibodies was done in a stepwise manner using the above test to determine an optimal panel for work-up of challenging lesions. Significance was set at $p<0.05$.

Results

Clinical findings

The patients' clinical and demographic findings are detailed in Table 2. Metastatic renal cell carcinoma to the adrenal included twice as many men as women, whereas primary adrenal lesions were slightly more common in women. All patients with metastatic renal cell carcinoma had a history of a kidney tumor; the adrenal lesions were not the first manifestations of disease.

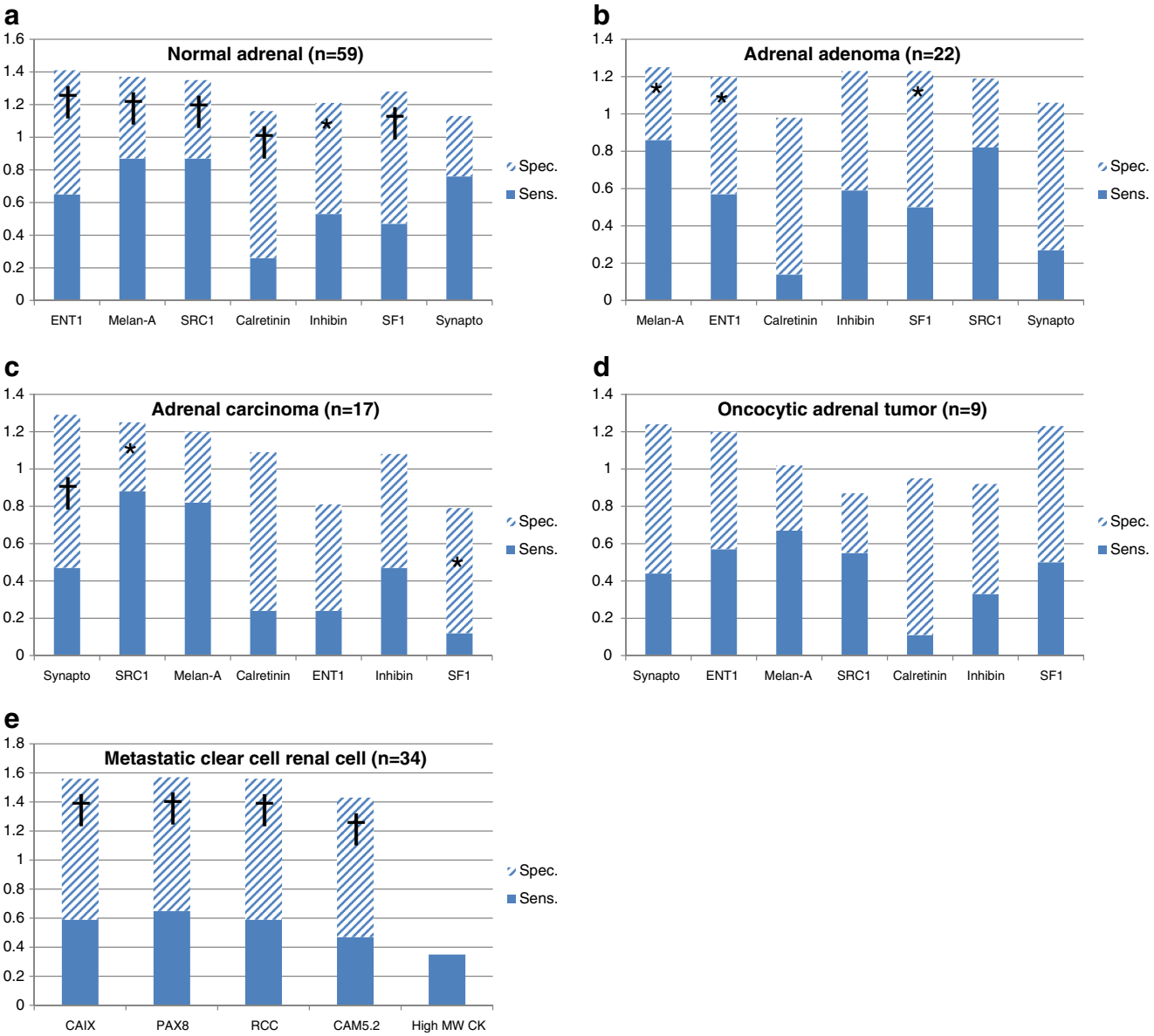

Fig. 1 Sensitivity and specificity of immunostains tested (**a**–**e**) using a ≥2+ reactivity cut point. By area under curve analysis: *$p<0.05$, †$p<0.001$

Pathologic findings

Histologically, the majority of the renal cell carcinomas were characterized on scanning magnification by an expansile, infiltrative mass composed of large cells with abundant clear cytoplasm. Focally prominent collections of red blood cells (blood lakes) could be seen in between epithelial structures.

Immunohistochemical findings

Results of immunohistochemical staining (Fig. 1) showed that the optimal markers for normal adrenal and primary adrenal lesions other than carcinoma (Fig. 2) were membranous ENT1, cytoplasmic MelanA, and nuclear SRC1. For normal adrenal, ENT1 was the most specific, while MelanA and SRC1 were the most sensitive. These three markers, along with calretinin and inhibin, were significantly discriminatory. Synaptophysin was inferior, and calretinin had low sensitivity, as did SF1, reflecting frequent equivocal to 1+ reactivity. Significant discriminators of adrenal adenoma were ENT1 and MelanA; SRC1 had rather lower specificity.

For adrenal carcinoma, synaptophysin, SRC1, and MelanA were significant discriminators (Fig. 3). Synaptophysin was most specific, while MelanA and SRC1 were again most sensitive. However, there was 2+ to 3+ SRC1 reactivity in 5 of 31 (16 %) cases of clear cell renal cell carcinoma and 1 of 3 papillary cases. Calretinin, ENT1, inhibin, and SF1 performed less well. For oncocytic tumor, synaptophysin was the best marker, with high specificity, while MelanA had the highest sensitivity but specificity of only 0.35. Calretinin had high 0.84 specificity but very low sensitivity.

In metastatic renal cell carcinoma to the adrenal (Fig. 4), membranous CAIX and RCC marker, nuclear PAX8, and cytoplasmic CAM5.2 were all highly specific and they discriminated renal cell carcinoma significantly. These markers stained about 70 % of tumors at the 1+ level, but the percent of cases with 2+ to 3+ reactivity was much lower. Cytokeratin 34βE12 had relatively inferior performances in sensitivity.

Positive and negative predictive values are shown for each stain (Table 3). Given the low positive predictive value of the adrenal stains for normal adrenal and adrenal lesions, there was an incentive to perform combinatorial analysis to determine the best model with two predictors for each diagnosis (Table 4). Overall results were similar to those with single markers, but the combination of CAIX and RCC marker maximized the area under the curve for detection of renal cell carcinoma.

Three markers were prone to nonspecific cytoplasmic biotin reactivity, and this presents a potential pitfall in diagnosis. Only membranous reactivity for CAIX and RCC marker and nuclear reactivity for PAX8 were counted as positive. Biotin cytoplasmic reactivity for PAX8 was noted in 84 % of normal adrenals, 0 % (0/2) adrenal hyperplasia cases, 82 % of adrenal adenomas, 82 % of adrenal carcinomas, 89 % of oncocytic tumors, and

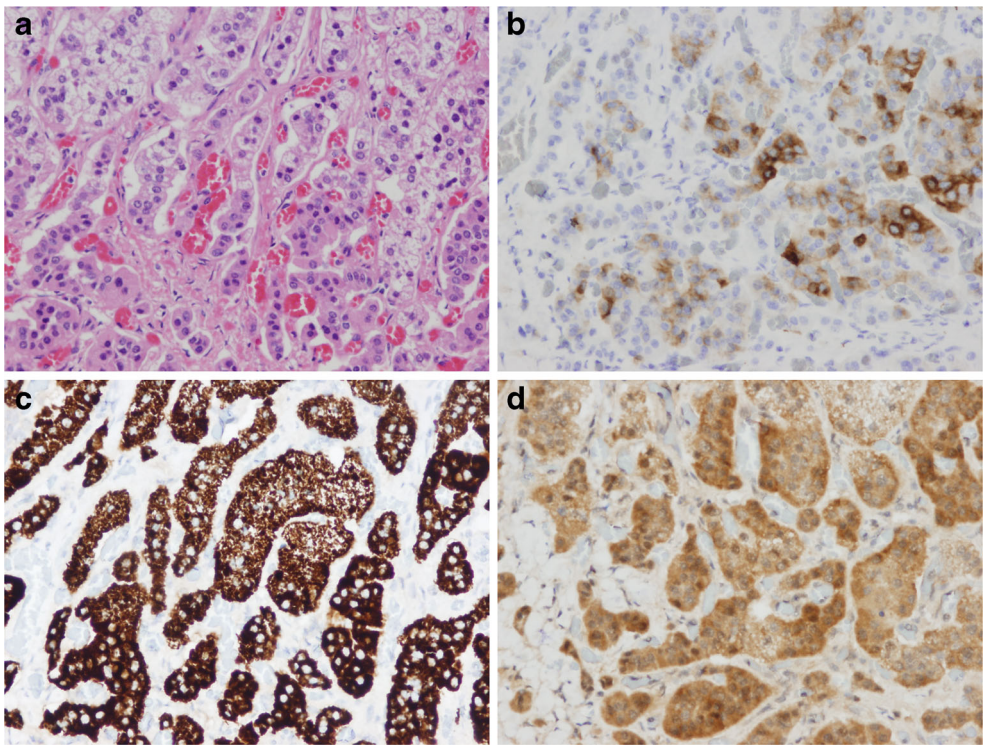

Fig. 2 Primary adrenal adenoma. **a**. H&E. **b**. Synaptophysin ≥2+ reactivity had 0.27 sensitivity and 0.79 specificity for adenoma. **c**. MelanA ≥2+ reactivity had 0.86 sensitivity and 0.39 specificity for adenoma. **d**. PAX8 cytoplasmic reactivity. 1+ to 3+ nonspecific staining was present in the cytoplasm of 82 % of adenoma cases. This was also true of many other adrenal lesions and clear cell renal cell carcinomas

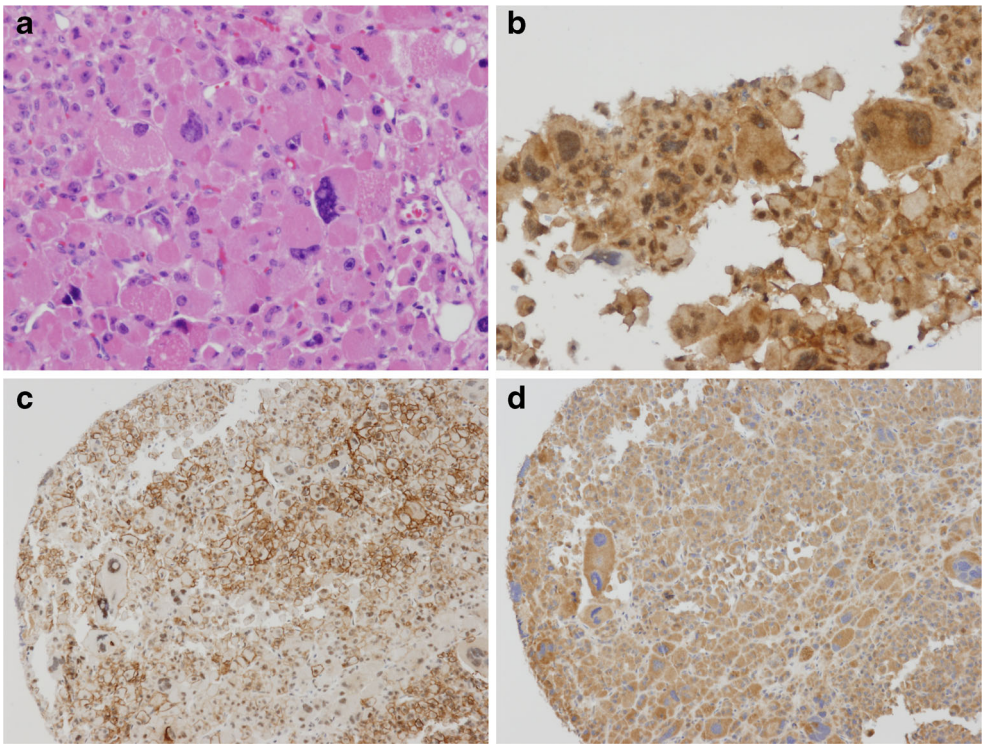

Fig. 3 Adrenal cortical carcinoma. **a**. H&E. **b**. Calretinin ≥2+ reactivity had 0.24 sensitivity and 0.85 specificity for adrenal cortical carcinoma. **c**. ENT1 ≥2+ reactivity had 0.24 sensitivity and 0.57 specificity for adrenal cortical carcinoma. **d**. CAIX cytoplasmic signal must not be called positive

47 % of clear cell renal cell carcinomas. CAIX had this problem in about 60 % of normal adrenals and primary adrenal lesions. RCC maker also had weak biotin signal in the cytoplasm of some adrenal lesions (Fig. 2d).

Discussion

Adrenal metastases from renal cell carcinoma are relatively infrequent but can be a source of diagnostic error, particularly

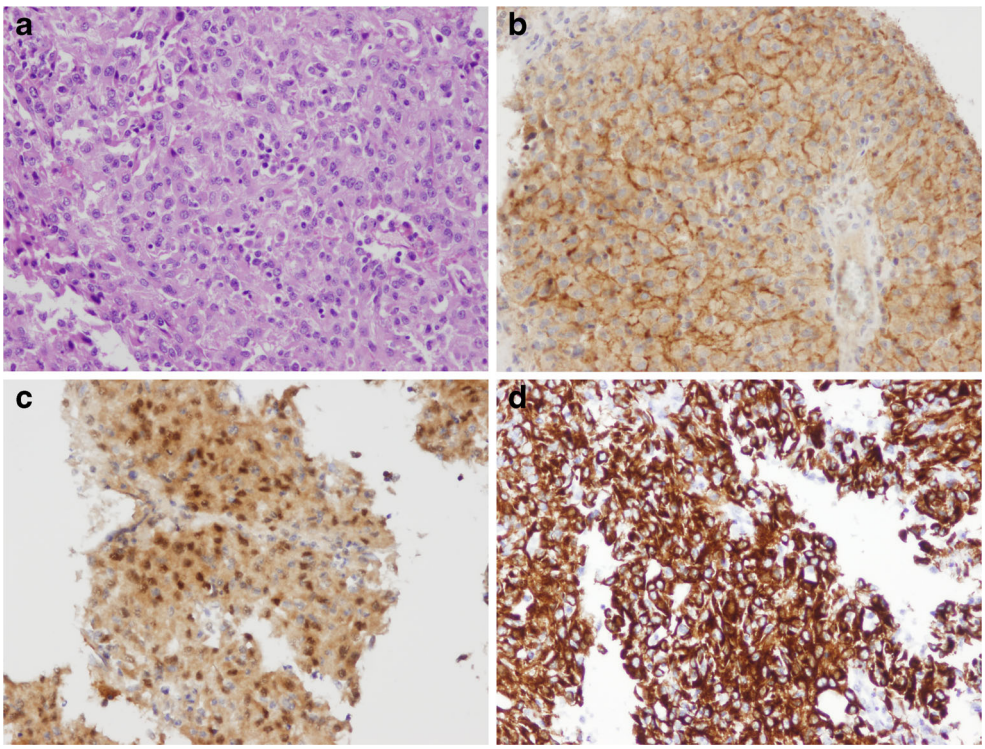

Fig. 4 Grade 4 renal cell carcinoma, metastatic to the adrenal. **a**. H&E. **b**. CAIX ≥2+ membranous reactivity had 0.59 sensitivity and 0.97 specificity for renal cell carcinoma. **c**. RCC marker ≥2+ membranous reactivity had 0.59 sensitivity and 0.97 specificity for renal cell carcinoma. **d**. PAX8 ≥2+ nuclear reactivity had 0.65 sensitivity and 0.92 specificity for renal cell carcinoma

Table 3 Positive and negative predictive values of markers (adrenal tissue versus renal cell carcinoma)

Marker	Normal adrenal		Adr. adenoma		Adr. carcinoma		Oncocytic tumor	
	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Calretinin	.64	.64	.14	.84	.18	.89	.05	.93
Inhibin	.53	.68	.24	.89	.15	.89	.06	.93
MelanA	.54	.85	.21	.94	.16	.94	.07	.94
Synapto.	.37	.59	.20	.85	.27	.92	.13	.95
SRC1	.53	.85	.20	.91	.17	.96	.06	.91
ENT1	.64	.77	.23	.89	.08	.83	.23	.89
SF1	.64	.67	.26	.88	.05	.84	.26	.88
Marker	Renal cell carcinoma							
	PPV	NPV						
CAIX	.87	.88						
PAX8	.73	.89						
RCC	.87	.88						
CAM5.2	.80	.85						
CK34βE12	.24	0						

PPV positive predictive value, *NPV* negative predictive value

in small biopsy samples. In recent years, immunohistochemistry has played an increasing role in the work-up of such lesions. We have studied 84 adrenal lesions and found that the most sensitive and specific renal cell carcinoma markers were CAIX, RCC, and PAX8. The optimal markers for adrenal cortical adenoma and normal adrenal were ENT1, MelanA, and SRC1; and for adrenal cortical carcinomas, they were synaptophysin, ENT1, and MelanA. This comprehensive study was limited only by use of tissue microarrays to evaluate reactivity; however, the sampling of tumor or benign foci that were spatially separate on the tissue block offset this limitation somewhat. The cost of evaluating 12 antibodies on whole sections would have been prohibitive.

Weissferdt et al. [1] recommended SRC1 and inhibin for the diagnosis of adrenocortical carcinoma, since these reacted with 97.5 % and 92.5 % of cases respectively: more than with calretinin, synaptophysin, or MelanA. SRC1 and inhibin also were sensitive markers of the myxoid variant of adrenocortical carcinoma [10]. However, the comparative reactivities of SRC1 and inhibin in renal cell carcinoma were not assessed in those studies. Here, we show that while SRC1 has excellent sensitivity for normal adrenal, adenoma, and carcinoma (Fig. 1a–d), its specificity was the lowest, because of frequent reactivity in renal cell carcinoma. Inhibin had better specificity, in the 0.60–0.70 range, but its sensitivity was in the 0.50–0.60 range. We also disagree with the recommendation [1] to include high-molecular weight cytokeratin in a diagnostic panel; we agree that while it almost never reacted with adrenocortical carcinoma, its sensitivity for renal cell carcinoma was low, at 0.35.

Sangoi et al. in 2011[8] studied 54 adrenal cortical neoplastic lesions compared with 5 metastatic renal cell carcinomas in the adrenal (among 185 total metastatic renal cell carcinomas).

Table 4 Optimal combinations of immunostains by diagnosis using ≥2+ reactivity cut-offs: best multivariate results

Diagnosis	Marker	Sensitivity	Specificity	*p* value	Notes
Normal adrenal	Sum of MelanA, c and ENT1, m	0.79	0.75	<0.0001	
Adrenal adenoma	MelanA	0.864	0.391	0.0242	1
Adrenal carcinoma	Synaptophysin, c	0.765	0.683	0.0003	1
Oncocytic adrenal tumor	N/A				No significant results
Renal clear cell carcinoma—metastatic	CAIX, m and RCC, m	0.82	0.95	<0.0001	2
	CAIX, m and PAX8, n	0.65	0.49	.02	
	RCC, m and PAX8, n	0.59	0.49	0.53	

p values from logistic regression with GEE

1 No better multivariate results were found. This is identical to the best univariate result

2 This is the best model with two predictors (markers) found in the data. However, since four markers were equally predictive, we do not have statistical power to make good comparisons of all possible combinations

c cytoplasmic, *m* membranous, *n* nuclear

The antibodies tested were calretinin, CD10, chromogranin, EMA, inhibin, MelanA, CAM5.2, RCC marker, synaptophysin, CAIX, PAX8, and SF1. We discovered ENT1 and SRC1 to be more robust markers of adrenal lesions than many of the adrenal-oriented antibodies they tested. They found that MelanA, calretinin, and inhibin had weak 1+, and sometimes even 2+, cytoplasmic staining in some metastatic clear cell renal cell carcinomas but that the addition of SF1 helped improve specificity. SF1, in our hands, showed frequent 0 to 1+ nuclear reactivity in adrenal lesions and was reactive in many renal cell carcinomas; thus both the sensitivity and specificity were inferior to ENT1 and SRC1. Our source for SF1 antibody was Santa Cruz and theirs was Dako, possibly accounting for a difference. We found calretinin reactivity in adrenal lesions less frequently than the 89 % figure of Sangoi et al. [8], and it tended to be 1+ in strength, not reliable for diagnosis. Our findings confirm their assignment of a 2+ threshold for MelanA and calretinin.

Sangoi et al. [8] also concluded that anti-PAX8 and anti-CAIX were among the most sensitive comparative markers for metastatic clear cell renal cell carcinoma but also included anti-human kidney injury molecule (hKIM-1) and hnf1b in that list; we did not test these since they are much less commercially available than the others. We also have reinforced the finding of Hu et al. who found that PAX8 was reactive in 93 % of renal cell carcinomas [11], although only 68 % of our metastatic renal cell carcinomas in the adrenal were reactive.

Some immunostains had nonspecific cytoplasmic biotin reactivity. CAIX is a hypoxia biomarker and a transmembrane protein. Only membranous staining for CAIX should be considered positive [12], and although it is less tissue-specific, it proved to be discriminatory in the context of adrenal lesions. RCC marker is a glycoprotein found in the renal proximal tubular brush border, and PAX8 is a nuclear transcription factor. These false-positive results, which occurred with CAIX and PAX8 in more than half of adrenal lesions, must not be overinterpreted as positive. Also, a few adrenal lesions had cytoplasmic biotin reactivity for RCC marker (Table 4). Renal cell carcinomas, too, had aberrant cytoplasmic reactivity. Likewise, Sangoi et al. also noted instances of cytoplasmic biotin reactivity for RCC and CAIX (and only with regard to clear cell renal cell carcinoma) [8], but did not describe this problem for PAX8, or of how adrenal cortical lesions reacted with these three antibodies.

Oncocytic adrenocortical tumors are composed entirely or predominantly of oncocytic cells with abundant cytoplasmic mitochondria. They are generally incidental findings and are not aggressive, and most are not functional [13]. In a series of 67 adrenocortical carcinomas, 6 were oncocytic adrenal carcinomas (11.2 %) [9]. We were fortunate to have access to 9 adrenal oncocytic tumors. Statistical analysis disclosed that ENT1 and synaptophysin were the two best-performing markers for oncocytic tumors, similar to the findings for other adrenal lesions. Nonspecific reactivity with many antibodies has been noted for oncocytic tumors in various locations, so this diagnosis warrants the use of multiple immunostains.

In summary, 34 clear cell renal cell carcinomas metastatic to the adrenal have been compared with 49 primary adrenal lesions. When the differential diagnosis is between primary adrenal carcinoma and its mimic, metastatic renal cell carcinoma, the recommended diagnostic panel should include two of the three stains for CAIX, PAX8, or RCC marker; and either SRC1 or MelanA. Synaptophysin must be used with caution because it consistently reacts with pheochromocytoma [2]. When the differential diagnosis is between normal adrenal or adrenal adenoma and nucleolar grade 1 (of 4) renal cell carcinoma, the diagnostic panel should include two of the three stains for CAIX, PAX8, or RCC marker; ENT1 and either SRC1 or MelanA. These optimal panels of immunohistochemical markers will be most useful with patients in whom a history of renal cell carcinoma is not available or if the tumor is occult.

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