

## CASE REPORT

### A “tumour trifecta:” Myelolipomata arising within an adrenocortical adenoma ipsilateral to a synchronous clear cell renal cell carcinoma.

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#### Abstract

We present an intriguing case of adrenal myelolipomata occurring within an adrenocortical adenoma in concert with an ipsilateral clear cell renal cell carcinoma. A 50-year-old female presented with dull right flank pain and hematuria. Computed tomography indicated a 2.5 cm right renal mass as well as a 5 cm right adrenal mass. Both masses were surgically resected concurrently. Histology of the renal mass was consistent with conventional clear cell renal cell carcinoma, Fuhrman grade III. There was no extra-renal extension or lymphovascular invasion. The adrenal mass was a cortical adenoma with solid and nested patterns, with discrete zones consisting of erythroid, myeloid and megakaryocytic cells intermixed with mature adipocytes. Mitoses were inconspicuous. The solid tumour component was strongly positive for vimentin, inhibin and CD56, focally positive for low-molecular-weight cytokeratin (Cam 5.2), calretinin and CD10 (chiefly in the myelolipomatous zones), and negative for chromogranin, S100, HMB-45, melan-A (A103), Mart-1, synaptophysin, SMA, CK7, CK20, ER, PR, TTF-1, CD99 and GCDFP (BRST-2). Ki67 (MIB1) staining indicated a low tumour proliferation index. Although well-described individually, a search of the English language literature suggests that this is the first such documented case of synchrony of these three lesions. We also present a relevant review of the literature pertaining to adrenal lesions. In particular, we emphasize the epidemiological, histological and immunohistochemical features that are helpful in determining the origin and malignant potential of adrenal lesions.

*Keywords:* myelolipoma, adrenocortical adenoma, clear cell carcinoma

#### INTRODUCTION

Adrenal lesions are surprisingly common,<sup>1</sup> so common are they in fact that radiological tools to assess the nature of so-called adrenal “incidentalomas” have been developed to reduce the cost and radiation burden that they frequently incite.<sup>2,3</sup> Suspicious lesions to the adrenal are metastases in most cases,<sup>3,4</sup> in fact, the adrenal is a site of metastasis in up to 30% of malignancies of various origins.<sup>5</sup> Adenocarcinomas are the most common metastatic lesion to the adrenal (56.3% of cases) and the most common site of origin of a metastasis was the lung (35.4% of cases).<sup>4</sup> In contrast, we present an intriguing adrenal lesion, occurring in concert with an ipsilateral renal cell carcinoma, demonstrating suspicious gross pathological findings but later found to constitute a benign primary adrenocortical adenoma containing multiple myelolipomatous foci.

#### CASE PRESENTATION

A 50-year-old female presented to her family physician complaining of persistent dull right flank pain and hematuria noted over several weeks. Her past medical history was notable for long-standing clinically stable multiple sclerosis, medically controlled hypertension, asthma, sleep apnea, irritable bowel syndrome and diverticular disease. In this instance, her physician was suspicious of a urinary tract malignancy and thus detailed imaging was ordered. Computed tomography indicated a 2.5 cm right renal mass suspicious for renal cell carcinoma as well as a 5 cm right central adrenal mass. She subsequently underwent surgical resection of the two masses concurrently. The procedure was tolerated well with the exception of a brief period of respiratory distress post-operatively, felt to be in keeping with her history of sleep apnea.

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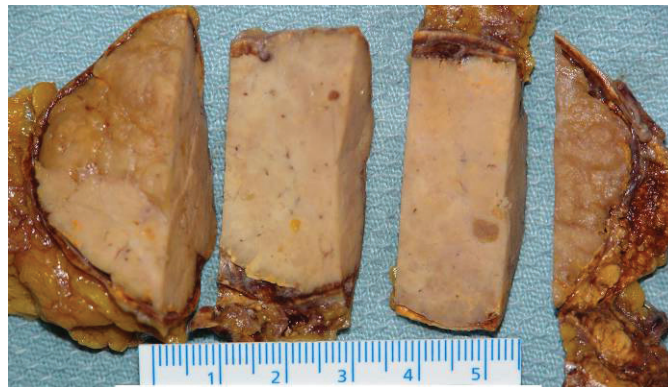


FIG. 1: Gross photograph (post-fixation) of adrenal tumour

#### Pathology

Examination of the surgical specimen revealed a 2.5 cm anterior mid-pole renal mass with chalky-yellow cut surface without gross evidence of extension beyond the renal capsule or into the renal pelvis or pelvic fat. There was no gross evidence of vascular extension. The adrenal gland was 7 cm in maximal dimension with weight 60 g. The cut surface demonstrated a 4.5 cm tan-gray nodule effacing the medulla but possibly originating from the cortex. The mass appeared to grossly abut a thin layer of normal adrenal cortex. A number of small areas of light-brown/yellow discoloration with myxoid consistency were noted in the parenchyma of the larger adrenal mass (Figure 1). The distinct gross appearance of the adrenal lesion raised suspicions of a primary adrenal tumour.

Histological examination of the renal mass (Figure 2) revealed a tumour showing solid and

tubulocystic architecture and consisting of large clear cells with variably enlarged nuclei as well as nucleoli prominently noted on intermediate power. A delicate intervening vasculature was also noted. The histological appearance was consistent with conventional clear cell renal cell carcinoma, Fuhrman grade III. There was no evidence of extra-renal extension or of lymphovascular invasion.

The adrenal mass was found to be chiefly composed of morphologically similar cells arranged in solid and nested patterns (Figure 3). The tumour cells showed minimal amphophilic cytoplasm with distinct hyperchromatic vesicular nuclei without prominent nucleoli. There were scattered pleomorphic cells, some showing a pronounced nuclear lobulation; some tumour cells were also multinucleated. Mitoses were inconspicuous, however, and no areas of necrosis or lymphovascular invasion were identified. The

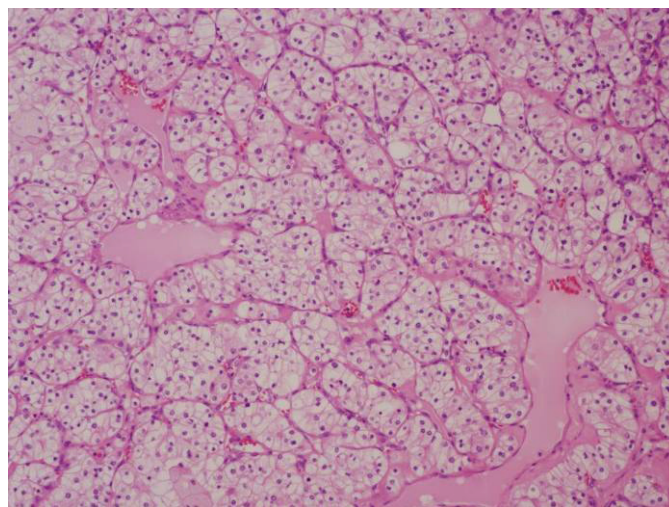


FIG. 2: Clear cell renal cell carcinoma (H&E, 100x)

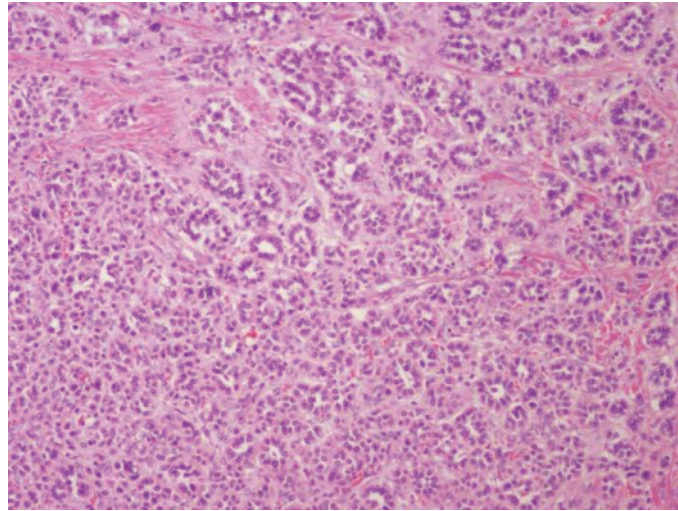


FIG. 3: Solid component of adrenocortical tumour (H&E, 100x)

light brown myxoid areas noted grossly were found to correspond to discrete zones with a distinctly different cell population (Figures 4 and 5); these consisted of a mixed population of erythroid, myeloid and megakaryocytic cells intermixed with mature adipocytes.

*Immunohistochemistry*

A number of immunohistochemical stains were requested (see Figure 6 for a select panel); the solid tumour component was strongly positive for vimentin, inhibin and CD56; it was focally positive for low-molecular-weight cytokeratin (Cam 5.2), calretinin and CD10 (chiefly in the myelolipomatous zones); it was negative for chromogranin, S100, HMB-45, melan-A (A103),

Mart-1, synaptophysin, SMA, CK7, CK20, ER, PR, TTF-1, CD99 and GCDFP (BRST-2). Ki67 (MIB1) staining also indicated a low tumour proliferation index.

**DISCUSSION**

Primary adrenal tumours are fairly common. It is well known that up to 25% of autopsy cases show incidental primary adrenocortical nodules.<sup>3,5</sup> Demographic data suggests an increasing incidence of adrenocortical adenoma with increasing age.<sup>3</sup> Although non-functioning adenomas are more common, functional adenomas are well-characterized aetiologic agents of hypercortisolism

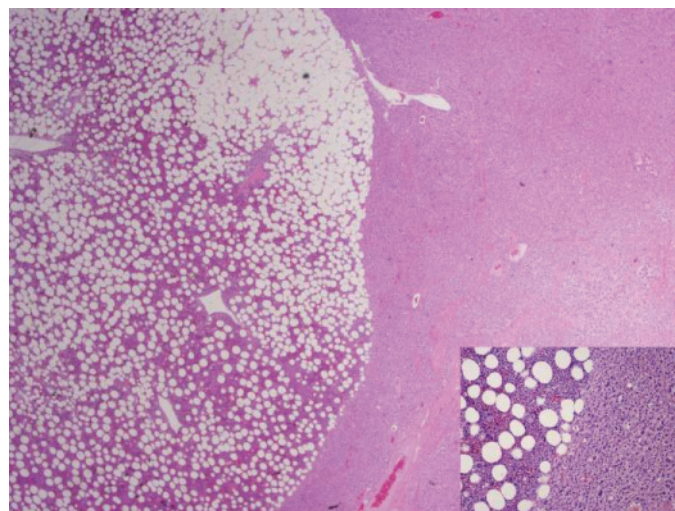


FIG. 4: Myelolipoma within adrenocortical tumour (H&E, 12.5x); inset, Myelolipoma-adrenocortical tumour interface (H&E, 100x)

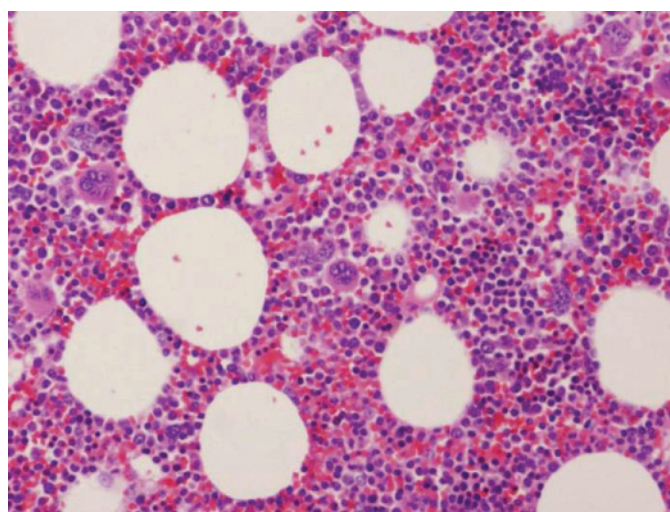


FIG. 5: High-power view of myelolipomatous component from adrenal cortex (H&E, 400x)

(Cushing’s disease), hyperandrogenism or hyperestrogenism (adrenogenital syndromes) and hypermineralocorticoidemia (Conn’s syndrome).

Adrenocortical adenomas are generally solitary, small (generally less than 5 cm in maximal dimension and rarely more than 50 g),

and unilateral lesions.<sup>3</sup> They are also classically described as showing a slow growth rate (i.e. showing less than 1 cm size increase per year), smooth outline relative to the surrounding tissues and generally show a homogeneous texture on both imaging and gross dissection.<sup>3</sup> Lesions identified in the adrenal cortex showing

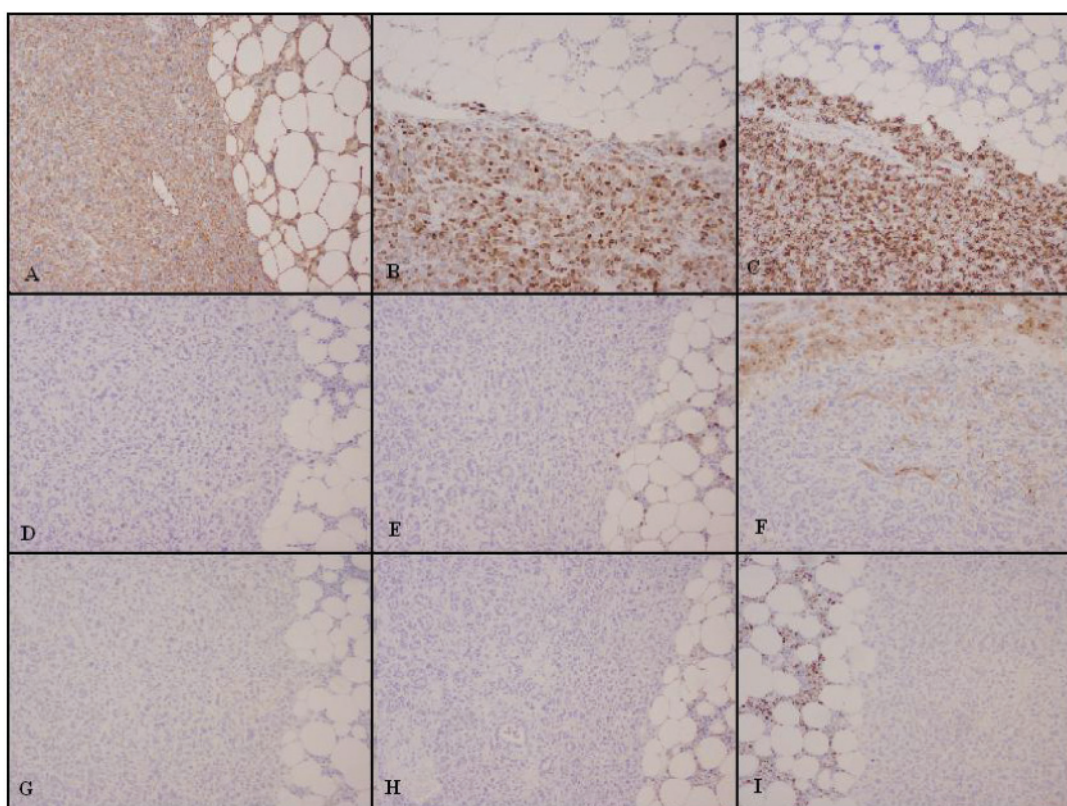


FIG. 6: Select immunohistochemical stains of adrenocortical tumour (All 100x): A – Vimentin, B- Inhibin, C- CD56, D-Cam5.2, E-CD10, F-Calretinin, G-Chromogranin, H-S100, I-Ki-67

radiological size greater than 4-5 cm, rapid increase in size over time, irregular outlines or areas of necrosis, internal haemorrhage or calcification should raise radiological suspicion of malignancy. Fortunately, the incidence of primary adrenocortical carcinoma is strikingly low, occurring at a rate of only 1 per million.<sup>1,5</sup> Nonetheless, primary adrenocortical carcinoma portends a poor prognosis; one recent study indicated a median survival of only 12-22 months.<sup>6</sup> This may be partly accounted for by the fact that only 30% of cases of primary adrenocortical carcinoma are isolated to the adrenal proper at initial diagnosis.<sup>6</sup>

As a result of the poor prognosis ascribed to adrenocortical carcinoma, it is incumbent on the surgical pathology team to examine any suspicious adrenal resection specimen with great care. Fortunately, a well-defined and verified system for histological assessment of adrenal neoplasia exists to identify lesions suspicious for carcinoma.<sup>5,7</sup> The Weiss system was recently reviewed and found, even many years after its development, to accurately identify lesions likely to correspond to adrenocortical carcinoma on the basis of three or more positive criteria, namely high nuclear grade using the Fuhrman approach, mitotic rate greater than 5 per 50 high-power-fields, the presence of atypical mitoses, a cellular complement of less than 25% of clear cells, a diffuse architectural pattern, identifiable necrosis or obvious invasion of either of vessels, nearby normal glandular sinusoids or of the tumour capsule.<sup>5,7</sup> Our case demonstrated a Weiss score of 2, supportive of a non-aggressive lesion, despite its relatively large size.

For those cases of questionable tumour origin, a panel of immunohistochemical stains has been shown to be helpful. Adrenocortical adenomas are frequently vimentin, calretinin, inhibin, melan-A and low-molecular-weight cytokeratin positive.<sup>5,8,9</sup> In deference to renal cell carcinoma, CD10 and D2-40 may be used to differentiate the two origins, adrenal lesions being more commonly negative.<sup>9,10</sup> Adrenal medullary lesions, also, are more commonly D2-40 positive relative to cortical lesions, and more commonly show positivity for neuroendocrine markers and negativity for keratins.<sup>5,10</sup> S100 protein may be useful if a nesting pattern is noted to highlight sustentacular cells.<sup>5</sup>

Approximately 4% of adrenal metastases can be expected from the kidney.<sup>4</sup> Furthermore, synchronous ipsilateral renal and adrenal tumours are typically malignancies of renal origin,

present in 1.2% to 10% of cases of renal cell carcinoma.<sup>11</sup> Despite this, however, renal cell carcinoma with ipsilateral adrenal metastasis makes up fewer than half of all synchronous adrenal and renal tumours.<sup>11</sup> The above make the process of distinguishing an adrenal adenoma from a primary adrenal malignancy challenging in some cases.

There are a variety of peculiar synchronous adrenal et al. tumours noted in the literature. A number of cases of renal cell carcinoma have been noted in synchrony with primary adrenal medullary lesions.<sup>11</sup> Also, a few cases of adrenocortical adenoma in synchrony with renal cell carcinoma have been encountered.<sup>12</sup> An even more remarkable case of synchronous pituitary adenoma and metastatic renal cell carcinoma has occurred, post excision of an adrenal adenoma also bearing a focus of metastatic renal cell carcinoma.<sup>13</sup>

Myelolipomata, though benign, are also uncommon.<sup>5</sup> They are most frequently noted in the adrenal incidentally (often on imaging), though a few symptomatic cases have been noted.<sup>5</sup> Only a few cases of adrenal myelolipomata occurring in synchrony with a renal cell carcinoma have been identified.<sup>14</sup> Likewise, although well described, there have been only a few cases of myelolipomata arising in adrenocortical adenomata.<sup>15</sup> A search of the English-language literature failed to demonstrate any cases of myelolipomata arising in an adrenocortical adenoma in synchrony with an ipsilateral clear cell renal cell carcinoma.

In conclusion, we present a fascinating "trifecta of tumours," which, although not rare on their own, present together likely constitute one of the few if any such documented cases. This case underlines the fact that, as demonstrated in the literature, adrenal tumours may take variable forms and may occur in concert with a variety of other disease processes.

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