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Adrenocortical Carcinoma Arising in an Adrenal Rest: a Case Report and Review of the Literature

Kristine M. Cornejo[1,2,3] · **Henrietta A. Afari**[4] · **Peter M. Sadow**[1,2]

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Abstract Carcinomas arising from embryonic adrenal rests are rare with only a handful of reported cases. We report a case of an adrenocortical carcinoma arising from an adrenal rest located between the bladder and prostate in a 51 year-old man. The patient presented following a year of rectal pain and constipation. Computed tomography (CT) scan revealed a 9 cm pelvic mass that appeared to arise from the soft tissue between the bladder and prostate, with displacement of the organs and narrowing of the rectal lumen, suspected to be a sarcoma. The surgically resected specimen showed a well-circumscribed, partially encapsulated tumor measuring 10.0 cm in greatest dimension. Both adrenal glands were identified intraoperatively. Grossly, the lesion was heterogeneous tan-brown to yellow, hemorrhagic and necrotic. Histology revealed sheets and nests of high-grade pleomorphic tumor cells with abundant clear to vacuolated cytoplasm with areas of necrosis, a high mitotic index (>10 mitoses/10 HPF) and foci suspicious for lymphovascular invasion. Adjacent adrenal cortical-type tissue was identified. Immunohistochemical stains revealed the tumor cells were weakly and focally positive for MiTF, Melan-A, inhibin and synaptophysin, and negative for CKAE1/AE3, HMB-45, calretinin, EMA, SMA, chromogranin, PAX8, MDM2 and CDK4. Based upon the morphologic and immunohistochemical profile, this was diagnosed as an adrenocortical carcinoma, arising in an adrenal rest. To our knowledge, no such tumor has been previously described in this location.

Keywords Adrenal rest · Adrenocortical carcinoma

✉ Kristine M. Cornejo
Kristine.Cornejo@umassmemorial.org

[1] James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA, USA

[2] Department of Pathology, Harvard Medical School, Boston, MA, USA

[3] Department of Pathology, UMass Memorial Healthcare, One Innovation Drive, Biotech 3, Worcester, MA 01605, USA

[4] Harvard Medical School, Boston, MA, USA

Introduction

Morgagni in 1740 first described yellowish nodules resembling adrenal tissue adjacent to the gland [1–3]. Over a hundred years later in 1856, Piccolominus was the first to report accessory adrenal tissue [2, 4]. Adrenal rests, also known as ectopic or accessory adrenal tissue are fragments that break-off during embryological development. The adrenal cortex arises from the coelomic mesoderm of the urogenital ridge and the medulla arises from neural crest tissue which invaginates into the cortical tissue during embryology [3, 5, 6]. Depending upon when the break occurs, determines what type of tissue will remain, such that closer to the gland proper will result in cortex with or without medulla and more distant to the gland will result in cortex only [3, 7].

Adrenal rests can occur anywhere along the embryological path of migration usually related to gonadal descent, such as in the retroperitoneum, kidneys, broad ligament, ovaries, spermatic cord, epididymis and testis. [2, 7] However, they have also been described elsewhere such as in intracranial and spinal locations and within the gastrointestinal system. [8–10] Adrenal rests are much more common in neonates and children (50%), and rarely persist into adulthood (1%) as functioning tissue or a neoplasm as it generally undergoes atrophy within a few years. [3, 6, 7, 11] However, it is exceptional for a malignancy to arise from an adrenal rest, with only a few cases reported. We present a case of an adrenocortical carcinoma

arising from an adrenal rest located between the prostate and bladder with a review of the English literature.

Case Report

A 51 year-old male with no significant medical history presented with rectal pain and constipation for 12 months duration. A computed tomography (CT) scan revealed a 9.0 cm pelvic mass that appeared to arise within the soft tissue between the prostate and bladder, causing organ displacement and narrowing of the rectal lumen. Based upon the radiologic features, it was suspected to be a sarcoma. A resection of the neoplasm was performed requiring dissection off both the bladder and prostate with a partial colectomy, due to adherence to the rectosigmoid colon. Both of the adrenal glands were identified intraoperatively and were grossly unremarkable.

The specimen showed a well-circumscribed, partially encapsulated tumor measuring 10.0 cm in greatest dimension. Grossly, the lesion was heterogeneous, tan-brown to yellow, hemorrhagic and necrotic. Histologic examination revealed sheets and nests of high-grade, pleomorphic cells with abundant eosinophilic to clear and vacuolated cytoplasm, with areas of necrosis and a high mitotic index (>10 mitoses/10 high-power field) (Fig. 1). Foci suspicious for lymphovascular invasion were also identified. Adjacent adrenal cortical-type tissue was also present, often in a lobular architecture. Immunohistochemical stains revealed the tumor cells were focally positive for MiTF, Melan-A, inhibin and synaptophysin. The tumor cells were negative for CKAE1/AE3, HMB-45, calretinin, EMA, SMA, chromogranin, PAX8, MDM2 and CDK4. Based upon the morphologic and immunohistochemical profile, this was diagnosed as an adrenocortical carcinoma (ACC), arising in an adrenal rest. The post-operative course was unremarkable, and he received adjuvant radiation and chemotherapy with mitotane. He had no evidence of disease at 9 months follow-up.

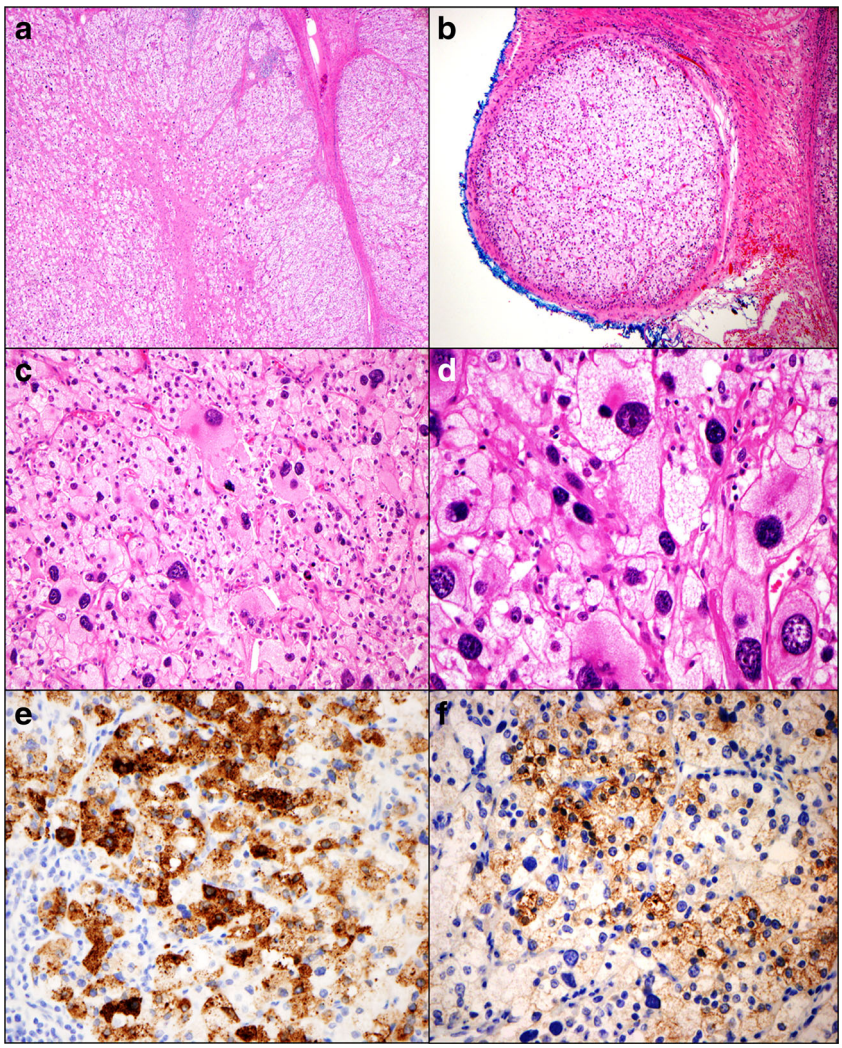

Fig. 1 AACC arising in an adrenal rest. a Low-power view of the lobulated architecture (H&E stain, ×20). b Background adrenal cortical-type tissue (H&E stain, ×20). c–d Sheets of high-grade, pleomorphic tumor cells with abundant eosinophilic and clear to vacuolated cytoplasm (H&E stain, ×100 and ×200). Tumor cells were focally positive for e Melan-A and f inhibin immunostains (×100)

Table 1 Summary of malignancies arising from an extra-adrenal rest (*n*=13)

Case	Age (y)	Sex	Location	Size (cm)	Wt. (gm)	Labs	Imaging	Initial Treatment	Follow-up
Wallace et al. [9]	23	F	Right liver	18	-	↑Serum testosterone, Δ4-androstenedione, cortisol, prolactin. ↑Urine 17-ketosteroid & 17-ketogenic steroids	Hepatomegaly with calcifications, irregular defects in right liver, both adrenal glands identified	-	DOD at 7 d post-admission due to large PE
Goren et al. [11]	50	F	Hilum of left kidney	8	150	WNL	Echogenic mass in medial lower half of kidney, displacing pelvicalcyeal system	Radical Nephrectomy	NED at 12 m
Yokoyama et al. [12]	34	F	Retroperitoneum	6.5	71	Serum and urine WNL for adrenal function.	Retroperitoneal mass between right kidney and IVC.	Resection	NED at 120 m
Akishima-Fukasawa et al. [13]	31	F	Retroperitoneum below left kidney, extending to aortic bifurcation (fused with aorta, IVC, jejunum, pancreatic tail, bilateral ureters,)	25	-	↑Serum cortisol & DHEA, ↓ACTH	Large retroperitoneal mass along the abdominal aorta, both adrenal glands identified.	CT × 1 m	Multiple mets including supraclavicular LN, left adrenal gland, liver, lung, bilateral ovaries, BM, pericardium, pleura & peritoneum, DOD at 16 m
Rodriguez et al. [14]	0.4	F	Spinal cord at T10-L2	6	-	No clinical evidence of endocrine dysfunction	Heterogeneously enhancing mass at T10-L2, both adrenal glands identified	Laminectomy with gross total resection	LR at 6 m s/p second gross total resection, undergoing CT (cisplatin, doxorubicin, etoposide, mitotane) 5 m post-op
Engel et al. [15]	3.4	M	Left testis	9		↑Urine 17-ketosteroid & 17-hydroxycorticosteroid	(Both adrenal glands identified intraoperatively)	Resection	Developed signs of adrenocortical insufficiency at 12 h post-op, LR at 4 months s/p RT, obvious mets at 9 months involving abdomen below kidney, lymph nodes s/p RT, pulmonary mets at 12 m & DOD at 13 m due to a CVA with severe HTN and coma of sudden onset
Morimoto et al. [16]	57	M	Left scrotum	5	50	ABNL glucose tolerance test, ↑urine 17-ketosteroid & 17-hydroxycorticosteroid	Tumorous density medial to left kidney (7 × 6 cm), left scrotal mass, bilateral lung densities, both adrenal glands identified	Laparotomy with removal of multiple masses medial to left kidney on renal vein and along abdominal aorta	DOD at 6 d post-op with tumor identified in the scrotum with mets involving the lung & retroperitoneum (identified at laparotomy)
Contreras et al. [17]	21	F	Right liver	12	450	↑Serum cortisol, 17β-estradiol, 17-OH-progesterone, progesterone, testosterone, $DHEASO_4$, ↑urine 17-ketosteroids, estrone-3α-glucuronide	Right liver mass, adrenal glands identified	Ketoconazole × 42 d followed by laparotomy	NED at 9 wks post-op

Table 1 (continued)

Case	Age (y)	Sex	Location	Size (cm)	Wt. (gm)	Labs	Imaging	Initial Treatment	Follow-up
Ney et al. [18]	59	M	Retroperitoneum 8 cm above right kidney at level of L1	7.5	98	↑Serum cortisol, hyperglycemia, ↑urinary steroids	(Prior laparotomy removed atrophic adrenal glands)	Laparotomy	-
Raith and Karl [19]	26	F	Cranial of left adrenal gland	15	-	↑Urine 17-ketosteroids, HCG (confirmed pregnancy)	Tumor in upper pole of left kidney, left adrenal gland identified	Resection followed by irradiation with cobalt	NED at 15 m
Bani-Hani [20]	52	M	Left retroperitoneum	19	1950	Adrenal function WNL	Retroperitoneal mass lying between spleen, stomach, tail of pancreas, splenic flexure & left kidney & adrenal gland	Resection	NED at 25 m
Jain et al. [22]	65	M	Left testis	8.5	-	↑Serum cortisol, ↓ACTH, hypokalemia, hypernatremia, hyperglycemia, ↑urine free cortisol level	Left testicular mass, right testicular mass (3.1 × 2.3 × 1 cm), mediastinal, supraclavicular & retroperitoneal LAD, retroperitoneal mass, both adrenal glands identified	Radical orchiectomy	Mitotane started 3 m post-op, DOD 2 m after last discharge with episodes of delirium
Current case	51	M	Pelvis	10	-	Adrenal function WNL	Pelvic mass arising within the soft tissue between the prostate and bladder, both adrenal glands identified	Resection followed by mitotane & RT	NED at 9 m

ABNL, abnormal; BM, bone marrow; cm, centimeters; CT, chemotherapy; CVA, cerebrovascular accident; d, days; DOD, died of disease; F, female; gm, grams; hrs, hours; HTN, hypertension; LAD, lymphadenopathy; LN, lymph nodes; LR, local recurrence; m, months; M, male; mets, metastasis; NED, no evidence of disease; PE, pulmonary embolism; post-op, post-operatively; RT, radiotherapy; s/p, status post; WNL, within normal limits; wks, weeks; y, years

Discussion

Tumors arising from adrenal rests are uncommon and most are functional, resulting in an endocrinopathy, and are often diagnosed pre-operatively [11]. Infrequently are they non-functional, usually discovered incidentally or at time of autopsy [11]. Malignancies arising from adrenal rests are extremely rare with only a handful of cases reported and their clinicopathologic features are summarized in Table 1 [9, 11–21]. Malignant tumors arising from adrenal rests have been described in 13 patients, including our current case at a mean age of 36.4 years (0.4–65 years) with an equal female to male ratio (7:6). The tumors were located in the retroperitoneum (*n*=5), testis/scrotum (*n*=3), liver (*n*=2), kidney (*n*=1), spinal cord (*n*=1) and pelvis (*n*=1). Eight (62%) tumors were functioning, with patients most commonly presenting with Cushing's syndrome.

Histologically, the differential diagnosis of ACC is broad and includes metastatic renal cell carcinoma (RCC), hepatoid variant of yolk sac tumor (YST), melanoma, malignant leydig cell tumor and liposarcoma [20]. Rarely, extra-adrenal neoplasms such as hepatic and Leydig cell tumors have been reported to produce ectopic cortisol, adrenocorticotropic (ACTH) and cortisol-releasing factor (CRF) [9, 22]. The pattern of immunohistochemical findings such as positive inhibin, Melan-A, MiTF and synaptophysin markers, suggest an adrenal cortex origin of the tumor cells and are expressed in ACC and help to exclude other malignancies in the differential diagnosis [20, 22].

Based upon our review of the literature, 11 of 13 cases (85%) underwent surgical resection with one case treated with chemotherapy alone (8%) and 5 (38%) cases treated with adjuvant chemotherapy and/or radiotherapy. Surgical resection is the mainstay of treatment with potential for cure in ACC [20, 23]. The 5 and 10-year survival in patients who underwent resection for ACC was 26–38% and 7%, respectively [23–25]. The patients with early mortality, were found to have higher rates of cortisol-secreting tumors, positive resection margins and higher stage with nodal or synchronous distant metastasis [23–25]. The importance of surgery was further confirmed by long-term survival attained with repeat resection of local or distant tumor recurrence [23].

In our review, 6 (50%) patients were diagnosed with tumor recurrence and/or metastases, of which 5 died of disease at a mean of 6.3 months (6 days-16 months) [9, 13–16, 22]. Five patients were without evidence of disease at a mean follow-up period of 26.4 months (2.25–120 months). All 5 patients underwent surgical resection for a primary tumor without evidence of nodal or distant metastasis, of which 2 were treated with adjuvant chemotherapy and/or radiotherapy [11, 12, 17, 19, 20].

The role of adjuvant chemotherapy and radiation is limited and unclear. Mitotane is the most common chemotherapeutic agent used to treat ACC with limited response [20, 26]. Tumors which do show response may obtain prolonged survival, with significant benefit found in patients not cured surgically or with an increased risk of recurrence [20, 25, 26]. Moreover, additional studies have found a significantly longer recurrence-free survival in patients treated with adjuvant mitotane therapy after radical surgery [26].

Adjuvant radiotherapy remains controversial with studies showing conflicting results, some revealing an advantage with significant reduction of local recurrence, while others showing no added benefit [27–29]. Functioning carcinomas with production of steroids may also benefit from treatment with agents such as ketoconazole by blocking adrenal steroid synthesis, such as the case reported by Contreras and colleagues [17].

The prognosis of patients with ACC is poor, with recurrence and metastasis being common [20, 26]. The management of patient's with more advanced disease in which surgical resection is not optional or curative may benefit from a combination of loco-regional resection, chemoembolization, radiofrequency (RFA) and/or systemic chemotherapy [26]. The combination of cytotoxic chemotherapy plus mitotane may also be beneficial in a subset of patients with advanced or metastatic disease with reduced progression-free survival [26].

Conclusion

In summary, we report the unique occurrence of an adrenocortical carcinoma arising from an adrenal rest within the pelvis, located between the prostate and bladder. Frank features of histologic malignancy were present. Although the occurrence of malignancies arising from adrenal rests is rare, pathologists should be aware that they can occur, particularly within any location along the path of embryologic migration of the genitourinary tract.

Compliance with Ethical Standards

Conflict of Interest None.

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