CASE REPORT

Primary adrenal angiosarcoma and functioning adrenocortical adenoma: an exceptional combined tumor

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Abstract

Context: Primary adrenal angiosarcoma is an extremely rare neoplasm, as are combined tumors within a given adrenal lesion.

Clinical presentation and intervention: A 35-year-old man presented with hypokalemic hypertension leading to the discovery of a 6 cm diameter malignant-appearing right adrenal tumor. The lesion displayed marked ¹⁸F-fluorodeoxyglucose uptake on positron emission tomography scanning. Endocrine investigations revealed secretion of both cortisol and aldosterone by the neoplasm. The entire right adrenal gland along with the periadrenal fat tissue was removed during laparoscopic surgery.

Results: Histological examination revealed two intermingled tumor cell proliferations, namely an angiosarcoma and an adrenocortical adenoma. An extensive post-operative search revealed no other primary tumor site, nor metastases. The lesion was then considered to be a primary adrenal angiosarcoma combined with a secreting adrenocortical adenoma. The patient received four cycles of chemotherapy (adriamycin/ifosfamide). At 2-year follow-up, he is alive and well, with no sign of relapse.

Conclusion: To the best of our knowledge, this is the first case of an adrenal neoplasm combining a primary angiosarcoma and a functioning adrenocortical adenoma.

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Introduction

Primary angiosarcoma of the adrenal gland (PAA) is an extremely rare neoplasm with only 25 cases reported so far in the literature (1–3). Most adrenal angiosarcomas represent metastases from another primary tumor site. Combined adrenocortical neoplasms are also rare entities. We report herein, to the best of our knowledge, the first case of a collision tumor associating a primary adrenal angiosarcoma and a bisecreting adrenocortical adenoma in a young man presenting with hypokalemic hypertension.

Case report

Clinical presentation

A 35-year-old Caucasian man presented to his physician with polyuria and asthenia. He reported

weight loss over the previous months. His medical history was unremarkable except for ankylosing spondylitis that was well controlled by non-steroidal anti-inflammatory agents (sulfasalazine and ketoprofene). General examination revealed high blood pressure (210/110 mmHg). No other physical signs suggestive of hypercortisolism were noted. Blood analyses showed low serum potassium level (2.9 mmol/l) and normal creatinine and fasting glucose levels. There was no anemia or abnormal white blood cell count. Ophthalmologic examination was unremarkable. Renal ultrasound examination did not reveal renal arterial stenosis but showed a 6 cm diameter right solid adrenal mass.

Hypertension was persistent on home blood pressure monitoring (average 163/95 mmHg) despite nifedipine treatment. Serum potassium level returned to normal after oral potassium intake. Endocrine investigations revealed secretion of both cortisol and aldosterone by

the adrenal mass. Supine and standing active renin levels were undetectable (normal, 10–25 mU/l); supine aldosterone and 24 h urine aldosterone excretion values were 593 pmol/l (normal, 80–400 pmol/l) and 117 nmol/day (normal, 14–47 nmol/day) respectively. Twenty-four hour urinary free cortisol level was 954 nmol/day (normal, 14–250 nmol/day). Plasma cortisol level was 497 nmol/l at midnight, and no response was observed after a 1 mg dexamethasone suppression test (plasma cortisol level at 246 nmol/l in the morning). Finally, plasma ACTH level was decreased (6 ng/l; normal, 10–60 ng/l).

Computed tomography (CT) scan of the chest and abdomen showed a 64 mm diameter heterogeneous mass of the right adrenal gland (Fig. 1). The lesion was characterized by a 28 Hounsfield Unit (HU) non-contrast attenuation value with marked vascularization after i.v. injection of contrast material (51 HU on the 1 min contrast-enhanced CT scan) without evidence of local tissue invasion or metastatic spreading. ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) scanning revealed a marked and exclusive ^{18}F -FDG uptake in the postero-superior aspect of the adrenal mass with a maximum standardized uptake value (SUV_{max}) of 9.7 and an adrenal-to-liver SUV_{max} ratio of 4 (Fig. 2).

After conditioning by spironolactone, the patient underwent a right laparoscopic adrenalectomy. Recovery was uneventful under cortisol supplementation. Spironolactone administration was discontinued immediately after surgery.

Pathological findings

The specimen measured 8×6×6 cm and weighed 126 g. On sectioning, there was a 6 cm diameter yellow lobulated mass that displayed large hemorrhagic and necrotic areas (Fig. 3A). The tumor appeared encapsulated. The residual adrenal gland measured 3×2×0.5 cm and was displaced laterally. Histopathological examination showed two intermingled tumor cell proliferations, one of which formed rudimentary vascular spaces. Those spaces were irregular in shape and communicated with one another in a sinusoidal

Figure 1 Computed tomography (CT) of the abdomen showing a 64 mm diameter heterogeneous mass (arrow) of the right adrenal gland without evidence of local tissue invasion. (A) Unenhanced CT scan. Non-contrast attenuation value was 28 Hounsfield Unit (HU). (B and C) Enhanced CT scan. After i.v. contrast material injection, attenuation value reached 51 HU.

Figure 2 ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) showing marked and exclusive ^{18}F -FDG uptake (arrow) in the postero-superior aspect of the adrenal mass with a maximum standardized uptake value (SUV_{max}) of 9.7.

fashion. Some vascular channels were lined by a single layer of highly atypical endothelial cells whereas in other areas the vascular spaces were lined by an excess of atypical epithelioid endothelial cells forming intraluminal buds (Fig. 3B). Red blood cells were observed within the vascular spaces. Atypical endothelial cells displayed high nuclear grade. They harbored large vesicular nuclei with prominent nucleoli. Mitoses were frequent. The lesion displayed large necrotic and hemorrhagic areas.

Intermingled with the angiosarcomatous lesion was an epithelial tumor composed of medium sized clear cells arranged in cords or nests. Atypia was minimal. There were no mitoses (Fig. 3C and D). The Weiss score was 0. There was no invasion of the periadrenal fat tissue by either tumor cell proliferation. On immunohistochemical analysis, the angiosarcomatous component expressed endothelial markers CD31, CD34, and less extensively, von Willebrand factor (factor VIII) (Fig. 3E). Aberrant expression of epithelial markers (low- and high-molecular weight cytokeratins (AE1/AE3)) by the tumor cells was also detected (Fig. 3F).

Thus, the lesion was a combined adrenal neoplasm comprised of a grade II angiosarcoma (French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) classification) and an adrenocortical adenoma with a Weiss score of 0.

Post-operative course

An extensive post-operative search including whole-body CT and FDG PET/CT revealed no other primary tumor site, nor metastases. The lesion was then considered to be a primary adrenal angiosarcoma

Figure 3 (A) Sectioning of the specimen revealed a 6 cm diameter yellow lobulated mass that displayed large hemorrhagic and necrotic areas. The residual adrenal gland was displaced laterally (arrow). (B and C) Rudimentary vascular spaces communicating with one another in a sinusoidal fashion. Some vascular channels were lined by an excess of highly atypical endothelial cells forming intraluminal buds (hematoxylin and eosin stain, $\times 100$). (D and E) Intermingled with the angiosarcomatous lesion was an epithelial tumor composed of medium sized clear cells arranged in cords or nests. Atypia was minimal and there were no mitoses. (F) Strong immunostaining of angiosarcoma cells for CD31. Note absence of staining of the intermixed adenomatous clear cells ($\times 100$). (G) Aberrant expression of cytokeratins (AE1/AE3) by highly atypical endothelial cells forming intraluminal buds.

combined with a secreting adrenocortical adenoma. Genetic analysis on the tumor specimen (comprising both angiosarcoma and adenoma tissues, $>70\%$ tumor cells overall) did not reveal loss of heterozygosity (LOH) at 17p13 or overexpression of IGF2 (11p15.5). Immunostaining for p53 protein was negative in both the angiosarcoma component and the adenoma component. The patient was referred to the French Sarcoma Group at the Gustave Roussy Institute where administration of adjuvant chemotherapy was decided to treat the sarcomatous disease. The patient received four cycles of an adriamycin/ifosfamide chemotherapy regimen. Cortisol supplementation was followed by glucocorticoids administration that is still ongoing because of the occurrence of a psoriasis bout. Thus, the post-operative hypothalamic–pituitary–adrenal function could not be assessed. After completion of treatment, CT scan and ^{18}F -FDG PET showed no residual disease. At 2-year follow-up, the patient is alive and well, with no sign of recurrence.

Discussion

PAA is an extremely rare neoplasm (1, 3). The first example of PAA was described by Kareti *et al.* in 1988 (4). The patient was a 54-year-old man presenting with abdominal pain and a left adrenal mass. The tumor recurred 7 months after initial surgery necessitating wide en bloc resection. PAA usually presents as an isolated adrenal mass either asymptomatic or causing non-specific symptoms like abdominal pain. In most cases, the lesion is >6 cm in diameter. Endocrine investigations are unremarkable and no definite diagnosis can be made preoperatively. On macroscopic

examination, the specimen usually displays extensive hemorrhage. On histopathological examination, PAA displays epithelioid differentiation with large, rounded neoplastic cells with vesicular nuclei and prominent nucleoli. On immunohistochemical analysis, the tumor cells express endothelial markers CD31, CD34, and von Willebrand factor (factor VIII). Immunostaining for epithelial antigens can be present, especially in epithelioid areas of the tumor; hence epithelioid angiosarcoma can be misdiagnosed as carcinoma (5).

Combined adrenal neoplasms (excluding metastatic lesions) are very rare. Most published cases were associations of pheochromocytoma with ganglioneuroma or ganglioneuroblastoma. Occasionally, pheochromocytoma was identified with malignant peripheral nerve sheath tumor (6). Adrenocortical adenoma has been described in association with myelolipoma (<20 cases published) (7), pheochromocytoma (8), adrenocortical carcinoma (ACC) (9), and hemangioma (10). Association between a primary adrenal angiosarcoma and an adrenocortical adenoma has never been reported before. PAA was diagnosed in a patient presenting with Cushing's syndrome but in this case, hypercortisolism was due to an ACTH-producing pituitary adenoma (11). The relationship, if any, between the two tumors is unclear. There is no known association between hypercortisolism and angiosarcoma development. Arsenic exposure has been implicated as a risk factor in angiosarcoma development in one study (12). In contrast to hepatic angiosarcoma, PAA has never been reported following vinyl chloride exposure.

In this case, several pre-operative findings were suggestive of a malignant neoplasm: multiple hormonal secretions (production of glucocorticoids and mineralocorticoids), tumor size >6 cm, an attenuation value higher than 10 HU on unenhanced CT scan, and a high ^{18}F -FDG uptake (3, 13–15). Recent studies demonstrated that a high ^{18}F -FDG uptake (an adrenal-to-liver SUV_{max} ratio over 1.45, 1.6, and 1.8 according to Groussin *et al.* (14), Nunes *et al.* (3), and Tessonnier *et al.* (15), respectively) was predictive of an aggressive neoplasm (3, 15). Interestingly, Nunes *et al.* (2010) (3) observed an adrenal-to-liver SUV_{max} ratio of 3.05 in an adrenal angiosarcoma which displayed heterogeneous unenhanced density. Thus, ^{18}F -FDG PET scanning may be a useful adjunct to assessing indeterminate adrenal masses in patients with no previous history of cancer.

Genetic analyses performed on the lesion did not show LOH at 17p13 or IGF2 overexpression. LOH at the 17p13 locus is detected in up to 30% of adrenocortical adenomas and in up to 87.5% of ACCs. Only 0–6% of adrenocortical adenomas display *TP53* mutations whereas about 25% of sporadic ACCs do so (16–18). LOH at the 11p15 locus (encompassing *IGF2* gene) has been observed in 34% of adrenocortical adenomas and in 67–83% of sporadic ACCs. IGF2 overexpression is

detected in 90% of ACCs (19, 20) and 25% of adrenocortical adenomas (6). *TP53* mutation and *IGF2* overexpression are associated with a worse prognosis in adrenocortical tumors, hence their role as molecular markers in those neoplasms to optimize patient therapeutic management (18). Germline mutations of *TP53* are identified in 70% of Li-Fraumeni families conferring susceptibility to soft tissue sarcomas and ACCs (21). In sporadic adrenocortical tumors, *TP53* mutation seems to be a late event in the malignant transformation process. The absence in this case of the above-mentioned genetic alterations concurs with the benign nature of the adrenocortical tumor. Apart from LOH analysis at 17p13, no specific genetic analysis was performed with regard to the angiosarcoma component. Specific genetic alterations have yet to be identified in angiosarcomas.

The role of laparoscopic adrenalectomy in adrenal cancer management is controversial. Three recent studies have reported a higher risk of peritoneal carcinomatosis associated with laparoscopic resection vs open adrenalectomy in ACC surgery (22–24). However, all these studies were retrospective in nature and included few patients with laparoscopic approach. Besides other studies showed opposite results, suggesting a comparable oncologic outcome for the two procedures (25, 26). Even though a diagnosis of ACC was suspected preoperatively, a laparoscopic procedure was chosen in the present patient for several reasons: the tumor appeared localized and measured <10 cm in diameter, and the surgeon was highly experienced in adrenal tumor surgery. On pathological examination, the neoplasm appeared encapsulated and the surgical margins were tumor-free.

Angiosarcoma is a locally invasive neoplasm. Direct invasion of adjacent organs has been described but involvement of the contralateral adrenal gland and occurrence of lung metastases have also been reported (4, 27–29). Complete surgical removal is the treatment of choice since radiation therapy and chemotherapy cannot achieve cure. Had the diagnosis of angiosarcoma been made preoperatively, an open anterior en bloc resection approach would have been chosen for this patient including the ipsilateral kidney and psoas muscle and an omentectomy (30). Nevertheless, because of R0 (no residual disease) post-operative status, young age of the patient and co-morbidity (ankylosing spondylitis requiring long-term treatment by non-steroidal anti-inflammatory agents with potential renal toxicity), a conservative renal strategy has been preferred with no re-intervention. Systemic chemotherapy is usually administered in locally recurrent or metastatic disease. In this case, adjuvant chemotherapy has been decided upon because of initial laparoscopic surgery and young age of the patient. In the largest series of primary adrenal angiosarcomas published, three patients were alive at the time of reporting (at 13-, 11-, and 6-year follow-up,

respectively), three had died from the disease, and three others had died from unrelated causes (27).

In conclusion, we report herein the first case of a combined adrenal tumor comprised a primary angiosarcoma and an adrenocortical adenoma. Endocrine anomalies, CT scan and ¹⁸F-FDG uptake characteristics were suggestive of a malignant neoplasm but even *a posteriori* there was no clue as to the presence of a primary angiosarcoma combined with an adrenocortical adenoma.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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