

Adrenal Oncocytic Neoplasm with Uncertain Malignant Potential

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ورم اونكوسايتوما للغدة الكظرية ذات السلوك الخبيث غير المؤكد

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الملخص: هي مجموعة من الأورام النادرة التي تصيب الغدة الكظرية غير معلومة التاريخ المرضي و السلوك المستقبلي. من ستة وأربعين حالة قد سجلت حتى الوقت الحاضر، ستة حالات فقط صنفت بناء على الفحص التشريحي المجهرى بأنها أورام ذات السلوك الخبيث الكامن. بدورنا نقدم حالة استثنائية لمريض ذكر يبلغ من العمر خمسة وثلاثين سنة مصاب بورم الغدة الكظرية الحميد ظاهريا مع بعض الخصائص الدالة على السلوك الخبيث الكامن

مفتاح الكلمات: أورام الغدة الكظرية؛ انكوسايتوما؛ ادرينال انسدادتالوما؛ عرض حاله؛ عمان.

ABSTRACT: Adrenal oncocytic neoplasms (AONs) are a rare group of tumours with a somewhat uncertain natural history and clinical behaviour. Out of 46 cases of AON reported to date, 6 cases were histologically classified as neoplasms with uncertain malignant potential. We report the case of a 35-year-old male with an incidentally-detected large AON with mostly benign morphology and some characteristics which would make its behaviour uncertain.

Keywords: Adrenal tumors; Oncocytoma; Adrenal incidentaloma; Case report; Oman.

ONCOCYTIC NEOPLASMS ARE RARE, predominantly benign neoplasms. They have been discovered in the kidneys, thyroid, parathyroid, salivary and pituitary glands, ovaries, and lungs. Adrenal oncocytic neoplasms (AON) are extremely rare. Oncocytomas are epithelial neoplasms composed of cells with abundant eosinophilic granular cytoplasm. Ultra-structurally, the component cells are packed with swollen mitochondria. They have non-functional neoplasm and, hence, are usually detected incidentally. However, one case exhibiting secretion of cortisol and testosterone was reported recently.¹

Case Report

A 35-year-old male presented having experienced chronic upper abdominal pain for a year and reported a history of headache, excessive sweating, and sleep disturbance. A physical examination was unremarkable except for high blood pressure. An abdominal computed tomography (CT) scan

showed a 12 x 9 x 5 cm left adrenal mass [Figures 1A & B]. His serum electrolytes, blood urea nitrogen, serum creatinine, and complete blood counts were all normal. His plasma normetanephrine level was 0.31 nmol/L (normal range [NR] ≥ 0.94), plasma metanephrine 0.17 nmol/L (NR ≤ 0.37), 24 hours urinary adrenalin >41 nmol/24h (NR = 3–109), urine noradrenaline 150 nmol/24h (NR = 89–473), and urine dopamine was 1260 nmol/24h (NR = 424–2612). Plasma rennin was 3.8 ng/L (NR = 3–16), aldosterone 219 pmol/L (NR = 21–413), serum prolactin 235 mIU/L (NR = 56–278), and serum chromogranin A was 2 ug/L (NR = 27–94). A metaiodobenzylguanidine (MIBG) scan showed no abnormal uptake. A diagnosis of a non-functioning left adrenal tumour was made.

Open trans-peritoneal exploration showed a well circumscribed 12 x 9 x 3 cm left adrenal tumour [Figure 2]. There were no enlarged lymph nodes and no other evidence of metastasis to suggest adrenal carcinoma. The right adrenal gland

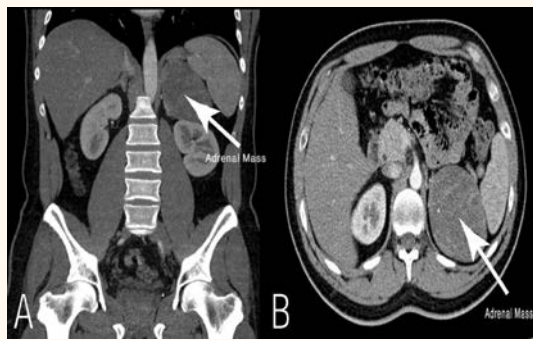


Figure 1 A & B: Abdominal computed tomography scans showing a 12 x 9 x 5 cm left adrenal mass (arrows).

was normal. A left adrenalectomy was carried out. Grossly, the outer surface of the 320 g tumour was smooth with intact capsule. The cut surface showed a solid grey-brown appearance with areas of haemorrhage. Sections of the tumour revealed a lesion that was mainly composed of spheroidal cells having granular eosinophilic cytoplasm and large vesicular nuclei [Figure 3].

These nuclei showed marked variation in size but no increase of mitosis. The cells also contained lipid vacuoles and eosinophilic globules. Some showed intra-nuclear and cytoplasmic vacuoles. The stroma showed focal oedema and myxoid changes with small areas of necrosis. There was no capsular or vascular invasion. The mitotic count was low and the tumour showed no overt malignant features morphologically. Immunohistochemical staining was positive for calretinin and inhibin [Figures 4A & B]. Focally, the tumour cells were positive for neuron-specific enolase but negative for chromogranin, AE1/AE3, S-100, and epithelial membrane antigens. An electron microscopic examination showed that the tumour cells contained mitochondria and scattered cytoplasmic vacuoles. The Ki-67 tumour marker test showed occasional mitotic figures. A morphological diagnosis of adrenal oncocytoma (AO) was made. However, the tumour exceeded 10 cm and weighed over 200 g, making this an AON with uncertain malignant potential (AONUMP).

The patient was discharged 4 days after surgery with no further treatment recommendations. The patient's follow-up included a physical examination and abdominal ultrasound every 6 months, for 24 months in total. There was no evidence or symptoms of recurrence. The patient was advised to continue with long term follow-up because of the

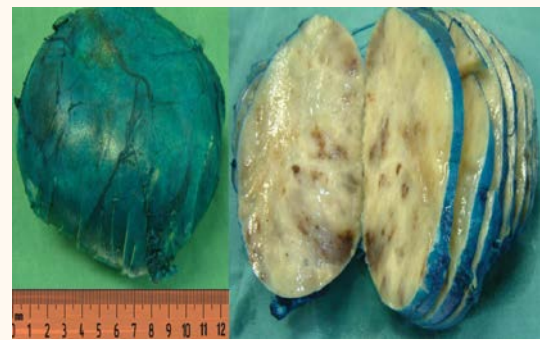


Figure 2: A well-circumscribed 12 x 9 x 3 cm left adrenal tumour. The outer surface was smooth with an intact capsule. The cut surface showed a solid grey-brown appearance with areas of haemorrhage.

possible malignant potential of the tumour.

Discussion

AONs are extremely rare with only 46 reported cases, including 24 AOs, 16 malignant oncocytic tumours, and 6 tumours with uncertain malignant potential.² Most of these tumours were detected incidentally upon imaging done to evaluate unrelated symptoms. Recent literature showed that the detection of "adrenal incidentalomas" (including adenomas, myelolipomas, cysts, ganglioneuromas, pheochromocytomas, carcinomas, or metastasis) had increased by 5% with use of high-resolution imaging.³ Most AONs are well-circumscribed, ranging from 2.2–15 cm, and weighing from 8–860 g (mean = 281 g). Studies have shown a female predominance (7:4) with a mean age of 43.5 years (range = 27–72 years).⁴ With the exception of two cases with heterotropic supra-

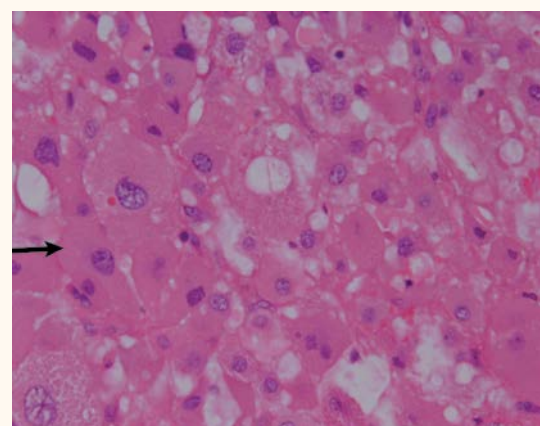


Figure 3: Tumour cells showing an abundant eosinophilic and granular cytoplasm with vesicular nuclei (haematoxylin and eosin stain; magnification x 400).

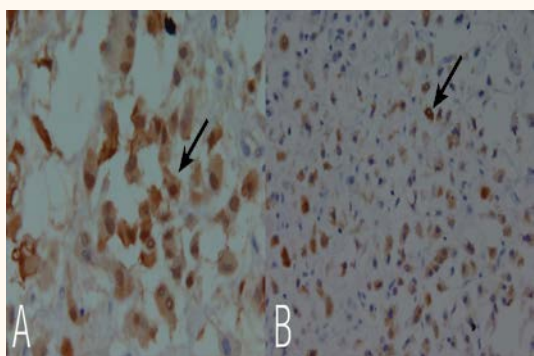


Figure 4 A & B: (A) Tumor cells show cytoplasmic and nuclear immunohistochemical staining for calretinin. (magnification x 400). (B) Tumor cells showing a positive immunoreactivity for inhibin (magnification x 200).

adrenal retroperitoneal tissue, and 6 symptomatic intraspinal oncocytic adrenocortical adenomas, all AONs were located in the adrenal glands with a left side predominance (7:5).⁵ Most of these tumours were non-functioning with the exception of one case which presented with Cushing's syndrome.⁴

AONs are mostly benign and generally small (<5 cm diameter and weighing <50 g). In 22 reported cases, no evidence of recurrence or metastasis was recorded after a follow-up period ranging from 1 to 99 months. Borderline AONs also seem to have benign clinical behaviours. Basceglia *et al.* reported 4 patients with AONs with uncertain malignant potential, with a mean follow up of 38.75 months (10–61 months) with no evidence of recurrence.⁶ Lin *et al.* also reported two patients with a mean follow-up of 15.5 months (12–19 months).⁴ However, some cases showed malignant potential which might not correlate with histological appearance.⁶ One locally invasive malignant case was reported with metastasis in the liver that invaded the inferior *vena cava*, although the microscopic appearance was that of a benign lesion with the absence of mitosis and nuclear pleomorphism.⁷

Benign adrenal cortical tumours are differentiated from malignant ones by examining macroscopic and microscopic features, as no other criteria seem to be predictive of their behaviour. Several histological systems have been proposed to predict the biological behaviours of adrenocortical tumours. The Weiss system uses histological criteria to differentiate benign adrenocortical tumours from malignant ones. If 3 or more of these features are present (nuclear grade III–IV; a mitotic rate of more than 5 per high-power field; atypical mitosis; a clear

cell tumour composition of less than 25%; diffuse architecture; the presence of necrosis, and venous, sinusoidal or capsular invasion), the tumour is regarded as malignant.⁸ The Weiss system recently was revised by Basceglia *et al.* to define clearly the terms adrenal oncocytic carcinoma (AOC), AONUMP, and AO.⁶ If the oncocytic tumour shows one or more major criteria (a mitotic figure of more than 5 mitoses per 50 high-power fields, any atypical mitosis, or any venous invasion), it is an AOC. If the tumour exhibits one or more minor criteria (a size of more than 10 cm and/or more than 200 g, necrosis, or capsular or sinusoidal invasion), it is AONUMP. If none of the described features is present, the tumour is AO. In our case, the tumour was considered borderline because of its size and weight.

Proliferative activity tests by Ki-67 and oncoprotein p53 have been used to predict the behaviour of adrenocortical tumours. The results of Basceglia *et al.* concerning the Ki-67 expression of AOC were almost in accordance with other studies for conventional adrenocarcinoma.⁶ Other studies showed that Ki-67 and p53 cannot be reliably used to predict the biology of AONs.^{4,9,10} Currently, morphological assessment remains the cornerstone of diagnosis and assessment of biological behaviour of adrenal cortical neoplasms.¹⁰

To our knowledge, the radiological features of AONs have been described in only 5 case reports in English medical literature.^{11–13} The findings were mostly homogeneous attenuation on non-enhanced CT. However, one case demonstrated a homogeneous mass with a central hyperdense area owing to haemorrhage, or central necrosis resulting in fibrous scarring which gave the appearance of a spoke wheel pattern. Contrast CT demonstrated mostly heterogeneous masses. Magnetic resonance imaging (MRI) demonstrated homogeneous and intermediate signal intensity on T1- and T2-weighted images with heterogeneous enhancement following gadolinium administration.¹²

Recently, ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) has shown great potential in differentiating malignant from benign adrenal lesions, and was used to evaluate an adrenal lesion in a patient known to have a hepatocellular carcinoma.^{9,14} The scan images showed intense hypermetabolism in the adrenal mass, which was diagnosed initially as a metastatic

lesion from hepatocellular carcinoma. However, the histopathological report was of an AO. Tumours known to have a false high uptake are pheochromocytomas and adenomas.⁹ Therefore, AOs might also result in a false-positive ¹⁸F-FDG-PET scan. Interestingly, renal oncocytomas also revealed an intense uptake on ¹⁸F-FDG-PET as they also have the presence of numerous intracellular mitochondria.¹⁵

The surgical approaches for excision of adrenocortical tumours are controversial. Indeed, there is evidence that laparoscopic excision has an advantage as a minimally invasive procedure, allowing quick recovery, low postoperative discomfort, and a short hospital stay.¹⁶ A retroperitoneal laparoscopic approach for large or potentially malignant adrenal masses can be performed safely by highly skilled laparoscopic surgeons and a conversion to open adrenalectomy should be considered if local invasion is observed during surgery.^{11,16} Oncological outcomes suggest that in the setting of adequate surgical resection, recurrence patterns relate more to disease-process biology rather than the surgical approach. Some authors contend that size, suspicion of malignancy, and locally invasive disease should not be considered an absolute contraindication to laparoscopic adrenalectomy.¹⁷ However, there is still controversy regarding the appropriateness of laparoscopy for the resection of large adrenal tumours (>6 cm), or oncocytic tumours of uncertain malignant potential, because of the high risk of complications and incomplete resections. This is partly attributed to a lack of experience with the high rate of loco-regional recurrence.¹⁸ Whereas some authors reported the feasibility of laparoscopic adrenalectomy for all benign tumours irrespective of size, in difficult cases, hand-assisted laparoscopic adrenalectomy is a good alternative.^{19,20}

Conclusion

Because of the low incidence of AONUMP, little is known in terms of the long-term behaviour of AO tumors. Hence, long-term clinical follow-up of the patient is required. There is an increasing trend toward the laparoscopic approach, even for large or potentially malignant adrenal tumours.

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