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Adrenal Oncocytic Phaeochromocytoma with Putative Adverse Histologic Features: a Unique Case Report and Review of the Literature

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Abstract Oncocytic phaeochromocytomas are exceedingly rare tumours. To date, there are three reported cases in the literature. This report describes a case of adrenal oncocytic phaeochromocytoma with unique features and malignant potential in a 68-year-old man. The patient presented with an incidental non-functional mass discovered on routine radiological investigation, which was subsequently excised. Histologically, the tumour cells showed oncocytic features with high-grade nuclear abnormalities and foci of extension to the peri-adrenal fat. Immunohistochemistry performed was positive for chromogranin, CD56, S-100 and p53 and negative for inhibin, HMB-45, EMA, AE1/AE3, Cam 5.2 and calretinin. Electron microscopy showed electron dense granules of neurosecretory type, which confirmed the diagnosis. The malignant potential of the tumour was assessed on available histologic scoring systems, which demonstrated a high malignant potential. However, no recurrence was detected after 5 years of follow-up. Compared to all the previously reported cases of oncocytic phaeochromocytoma, this patient was the oldest on presentation, was the only case with identified high malignant potential and has the longest follow-up. A review of the literature showed that all the oncocytic phaeochromocytomas reported were non-functional, non-metastasizing and were described in women. To conclude, oncocytic phaeochromocytoma should be in the differential diagnoses of oncocytic tumours of the adrenal gland. Additional studies are needed to predict the behaviour of this entity.

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Introduction

Phaeochromocytomas are rare neoplasms of the chromaffin cells derived from the embryonic neural crest and are located in the adrenal medulla. It accounted for approximately 10 % of primary adrenal tumours [1]. The term extra-adrenal paragangliomas is used to describe extra-adrenal tumours of the sympathetic and parasympathetic nervous system in sites like carotid body, ear (jugulotympanic), retroperitoneum and urinary bladder [2, 3]. Composite tumours may rarely occur as both neuroendocrine and neural tissues are noted in the location. They are usually larger and noted in older patients [4, 5].

Oncocytic tumours are characterized histologically by cells with eosinophilic granular cytoplasm and ultra-structurally by the presence of numerous closely packed mitochondria. Oncocytic tumours of the adrenal gland were first described by Kakimoto and colleagues in 1986. The case was a non-functional adrenocortical adenoma with oncocytoma-like appearance [6]. Oncocytic adrenal tumours remain rare tumours since then. Mearini and colleagues have recently reviewed 147 oncocytic adrenal tumours in the literature [7]. In this review, the oncocytic adrenal cortical neoplasms were often non-functional, non-metastasizing and frequently described as incidental findings. Although mostly non-metastasizing, approximately one in five cases of these tumours exhibited elements of malignancy. Oncocytic phaeochromocytomas are exceedingly rare. There is only one case mentioned in the review by Mearini and colleagues. We report a case of oncocytic phaeochromocytoma with unique features and review the literature of this rare entity.

Case Report

Clinical Presentation

A 68-year-old gentleman presented with an incidental finding of a left adrenal mass on ultrasonographic examination. The patient only had a history of moderate hypertension, controlled with diuretics. CT abdomen revealed a 42-mm moderately enhancing non-homogenous left adrenal mass with clearly defined margins. No other masses or metastatic deposits were noted. Pre-operative biochemical evaluation of a 24-h urine collection showed normal levels of vanillylmandelic acid, adrenalin, nor-adrenalin, metadrenalin and nor-metadrenalin. Also, plasma metadrenalin, nor-metadrenalin, aldosterone, cortisol, ACTH and renin were all within normal limits. The pre-operative diagnosis was a non-functional adenoma. Surgical excision of the tumour was recommended.

Pathologic Findings

Macroscopic examination of the excised left adrenal mass revealed that it measured 45×35×35 mm and weighed 36 g. The tumour had a solid light brown cut surface, occasional cystic areas and firm consistency (Fig. 1). Histologically, the tumour was noted in the adrenal medulla and composed of diffuse solid and cystic arrangement of cells with oncocytic appearance, characterized by eosinophilic granular cytoplasm and single nuclei with prominent nucleoli. Myelolipomatous metaplasia was also present. The tumour has high-grade nuclear abnormalities, including nuclear hyperchromasia, moderate nuclear pleomorphism, intranuclear pseudoinclusions and vesicular changes. It also showed foci of capsular invasion

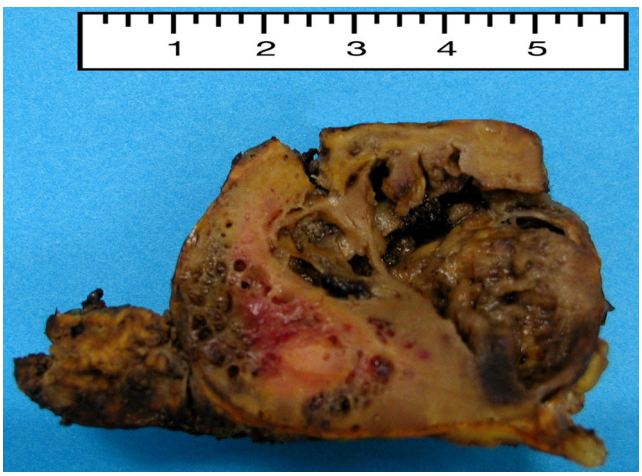

Fig. 1 Macroscopic features of the adrenal tumour. Gross examination shows a medullary lesion that has a light brown cut surface with some cystic areas

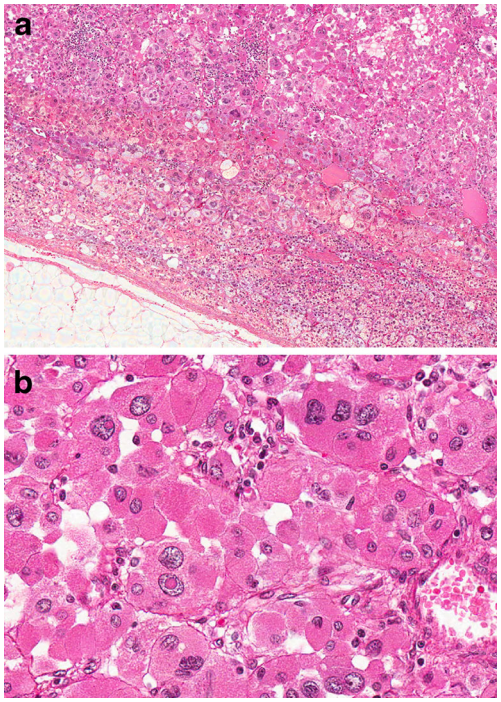

Fig. 2 Microscopic features of the adrenal tumour. **a** The tumour is located in the medulla with arrangement of cells showing diffuse sheets of tumour cells with eosinophilic granular cytoplasm and hyperchromatic nuclei (haematoxylin and eosin ×4). **b** At higher magnification, there are high-grade nuclear abnormalities, nuclear hyperchromasia, intranuclear pseudoinclusions and vesicular changes (haematoxylin and eosin ×20)

and extension into the peri-adrenal fat (Fig. 2). No other neural components (ganglioneuroma, ganglioneuroblastoma, etc.) were noted.

A paraffin block from the tumour was selected for immunohistochemical studies (Table 1). The tumour showed marked positivity for chromogranin and CD56 (Fig. 3a, b). It was focally positive for S-100 (Fig. 3c). In addition, p53 was strongly positive in the nuclei of the tumour (Fig. 3d). The proliferative index of the tumour as determined by Ki-67 was approximately 5 % (Fig. 3e). The counting was done on the most intensively stained area under ×40 magnification. It is negative for inhibin, EMA (epithelial membrane antigen), HMB-45 (human melanoma black), cytokeratins (AE1/AE, Cam 5.2) and calretinin. Electron microscopy showed numerous closely packed mitochondria and electron dense, membrane-bound granules with neurosecretory features (Fig. 4).

Considering the results of immunohistochemistry and electron microscopy, a diagnosis of adrenal oncocytic phaeochromocytoma was made.

Clinical Follow-up

Post-operative catecholamine levels taken at 6, 14 and 20 months after the operation were within normal limits.

Table 1 Antibody specifications and concentrations used

Antibody	Supplier	Country	Clone	Antigen retrieval	Dilution	Control tissue	Staining pattern
Calretinin	ZYMED	San Francisco, USA	Polyclonal	ER2 30 min	1:30	Colon	Cytoplasmic and nuclear
Cytokeratin	DAKO	Glostrup, Denmark	AE1/AE3	E1 10 min	1:200	Colon	Cytoplasmic
Cytokeratin	BD	San Jose, USA	Cam 5.2	E1 10 min	1:20	Colon	Cytoplasmic
Chromogranin A	DAKO	Glostrup, Denmark	DAK-A3	ER2 20 min	1:100	Pancreas	Cytoplasmic
EMA	DAKO	Glostrup, Denmark	E29	None	1:200	Lung	Membrane and cytoplasmic
HMB-45	Leica	Wetzlar, Germany	HMB-45	ER2 30 min	1:50	Melanoma	Cytoplasmic
Inhibin alpha	AbD Serotec	Kidlington, UK	R1	ER2 30 min	1:20	Ovary	Cytoplasmic
Ki-67	DAKO	Glostrup, Denmark	MIB-1	ER2 20 min	1:50	Tonsil	Nuclear
p53	DAKO	Glostrup, Denmark	DO-7	ER2 10 min	1:700	Colon cancer	Nuclear
S100	DAKO	Glostrup, Denmark	Polyclonal	E1 5 min	1:5000	Melanoma	Nuclear and cytoplasmic
CD56	ZYMED	San Francisco, USA	123c 3	ER2 30 min	1:100	Small cell lung carcinoma	Membrane

NB. All dilutions to be made up with antibody diluent (Leica Miscrosystems, AR9352);
ER2 epitope retrieval solution 2 (pH 9.0) (Leica Microsystems, AR9640), *E1* enzyme 1 (Leica Microsystems, AR9551)

Follow-up CT scan abdomen at 6, 13, 20 and 53 months showed no evidence of recurrent tumour. The patient was alive without clinical recurrence 5 years after the operation.

Discussion

In the English literature, three cases of oncocytic phaeochromocytoma (one from PubMed and two from

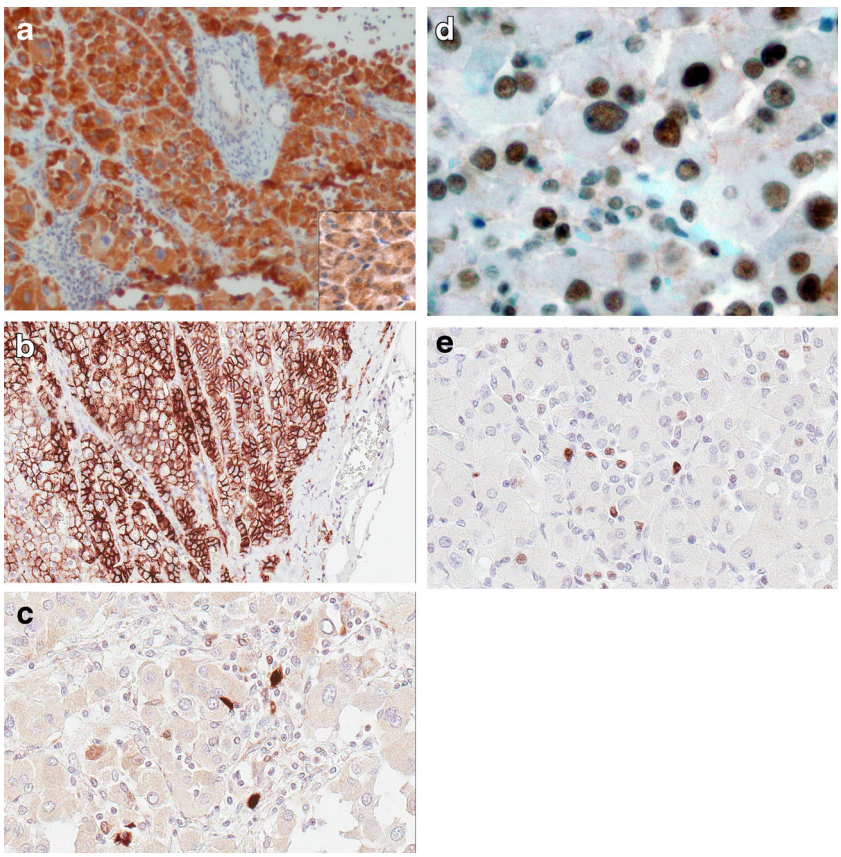

Fig. 3 Immunohistochemical staining. The tumour cells were positive for **a** chromogranin, **b** CD56, **c** S-100, **d** p53 and **e** Ki-67

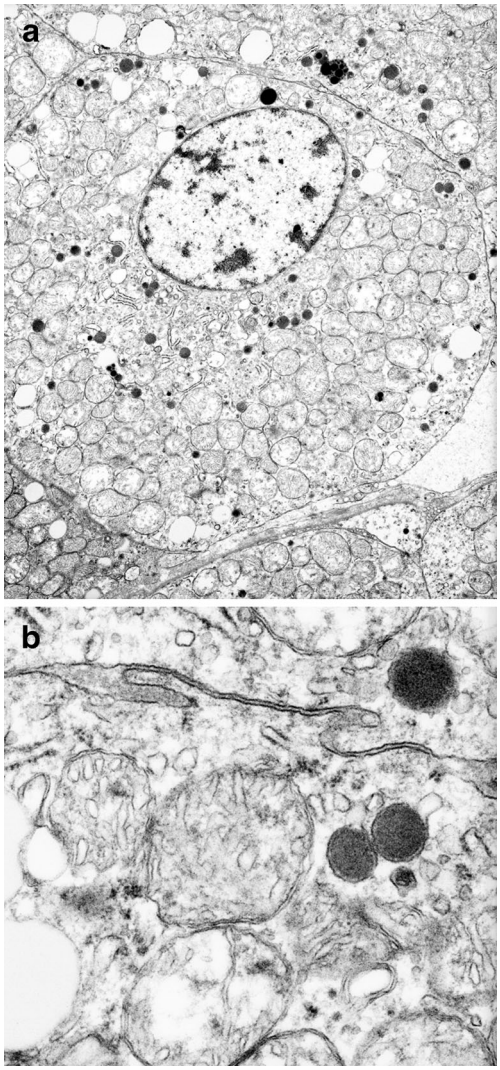

Fig. 4 Electron microscopy. **a** Ultra-structurally, the tumour shows large number of closely packed mitochondria and electron dense, membrane-bound granules. **b** Higher magnification of the granules

Google Scholar searches) were previously reported [8–10]. The first well-recognized case labelled as oncocytic phaeochromocytoma was described in 1997 by Wang and colleagues [8]. It is worth noting that oncocytic features in phaeochromocytoma have been briefly mentioned but not reported in details prior to that [11, 12].

All of the cases, in addition to our case, were considered non-functional and were found incidentally during a routine radiological investigation. It is worth noting that phaeochromocytoma is potentially fatal and hypertensive complications accounted for a significant proportion of the cases before or after the operation [13]. Blood and urine catecholamine metabolite measurements were performed in three of the four reported cases and were within normal limits. It is likely that the non-functionality of oncocytic tumours lies in the nature of oncocytic changes, which represent a cellular degenerative phenomenon with compensatory mitochondrial accumulation as a response to oxidative phosphorylation uncoupling [14].

Table 2 summarized the features of oncocytic phaeochromocytoma in the literature. Three of the patients had left-sided tumours and one had a right-sided tumour. All the previous cases occurred in females. The present case is the only case noted in a male. The age range of the patients was 36 to 68 years. In the literature, phaeochromocytomas mostly occurred in the third to sixth decades [15]. In the oncocytic phaeochromocytomas, the two earlier cases occurred in the fourth decade. The cases presented by Shibamori et al. and by us were detected in the seventh decade [10]. In fact, the current case is the oldest patient at the time of presentation. Further cases needed to be studied to address whether oncocytic phaeochromocytoma occurs in a later stage of life, similar to other lesions with oncocytic changes elsewhere.

The most likely clinical and pathological differential diagnoses of the current adrenal lesion are metastatic melanoma, hepatocellular carcinoma, renal cell carcinoma and adrenal cortical neoplasms. The former three differentials could be easily excluded by clinical and immunohistochemical studies. Adrenal cortical neoplasms were the major differential diagnoses for the current lesion. The differential diagnosis should be sorted out by both immunohistochemical and ultra- structural analyses. Adrenal cortical tumours are often positive for SF-1 and inhibin. However, SF-1 is not commonly available and performed whereas inhibin negativity may be seen in some adrenocortical tumours [16, 17].

In the present case, a rim of cortical tissue was noted and the tumour was located in the medulla (Fig. 2). In addition, based on the immunohistochemical reactivity for

Table 2 Features of oncocytic phaeochromocytoma reported in the literature

Author/year/country	Sex/age	Side	Presentation	Functional	Weight	Size	Follow-up	Remarks
Wang/1997/USA	F/38	L	Acute abdominal pain	No	275 g	34 mm	Nil	Areas of haemorrhage, cytokeratin+
Li/2000/USA	F/37	L	Increase abdominal girth	No	1150 g	170 mm	20 months	–
Shibamori/2013/Japan	F/61	R	Incidental finding	No	260 g	100 mm	13 months	–
Kasem/2014/Australia	M/68	L	Incidental finding	No	36 g	45 mm	5 years	p53+

M male, *F* female, *R* right, *L* left

Table 3 Histological features of the case according to the PASS score

Histological features	Tumour score	Maximum score
Large nests or diffuse >10 % growth	2	2
Central or confluent tumour necrosis	0	2
High cellularity	2	2
Cellular monotony	2	2
Tumour cell spindling	0	2
Mitotic figures	0	2
Atypical mitotic figures	0	2
Extension into adipose tissue	2	2
Vascular invasion	0	1
Capsular invasion	1	1
Profound nuclear pleomorphism	1	1
Nuclear hyperchromasia	1	1
Total PASS score	11	20

neuroendocrine markers (chromogranin and CD56), negative reactivity to inhibin and the ultra-structural findings of dense membrane-bound granules, the diagnosis of a phaeochromocytoma was made. No other components suggestive of a composite phaeochromocytoma were present.

One feature worth noting is the presence of foci of myelolipomatous metaplasia in the tumour. This morphology is more commonly seen in cortical adenoma, but it has also been described in pheochromoyctoma [18].

The malignant potential of phaeochromocytoma is known to be difficult to be predicted. In the literature, there are two major scoring systems. These include the PASS (phaeochromocytoma of adrenal scaled score) by Thompson based only on histological criteria and a Japanese scoring system based on histological criteria plus Ki-67 immunoreactivity and types of catecholamine produced by Kimura and colleagues [19, 20].

None of the previous cases reported in the literature have been scored on their malignant potential based on either of these two scoring systems, and immunohistochemichal staining for Ki-67 or p53 was not performed. Nevertheless, from the microscopic descriptions noted, they are likely to fall under the low-risk category. Li and Wenig reported no recurrence after a short-term follow-up of 22 months. Other than this, none of the other two cases had follow-up information [8–10].

In the present case, a PASS score of 11/20 was calculated (Table 3). As any tumour that scores >6 on this scale is considered to have a risk of metastasis, the tumour described in this study falls certainly under this category. If the tumour was scored according to the Japanese criteria, it would fall under the moderately differentiated category, carrying a borderline malignant potential. Thus, this is the first report of an adrenal oncocytic phaeochromocytoma case with aggressive histological parameters based on available scoring systems. Also, this is the only case with long-term clinical follow-up of over 5 years with no clinical recurrence, despite the presence of these adverse histological parameters. It is also worth noting that oncocytic adrenal cortical tumours, as compared to conventional adrenal cortical tumours, have a different system of assessment of malignant potential [21].

In phaeochromocytoma, when applying the available scoring systems to the present case, the present tumour would be in the borderline malignant category. Thus, more studies should be conducted to assess whether the histological scores for phaeochromocytoma are applicable in the settings of oncocytic phaeochromocytomas.

Recently, many newly discovered genes have been implied in the pathogenesis and as predictive markers in phaeochromocytomas and paragangliomas [22, 23]. The non-specific biomarkers like p53 have been reported in non-metastasizing and malignant phaeochromocytomas [24]. In the present case, p53 was diffusely positive which was consistent with the adverse pathological parameters noted.

In summary, a case of oncocytic phaeochromocytoma was reported and the features of three previously reported cases were reviewed. This is the first case illustrating adverse pathological parameters in an oncocytic phaeochromocytoma. Oncocytic phaeochromocytoma should be in the differential diagnosis of oncocytic tumours in the adrenal gland. More information is needed to assess the malignant potential of this entity.

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