CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

A Case of Retroperitoneal Liposarcoma Mimicking an Adrenocortical Carcinoma

Waye Kang,[1] Carolina Singarayar,[2] Nurasyikin Abdul Wahab,[2] Norlela Sukor,[2] Nor Azmi Kamaruddin[2]

[1]*Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Malaysia*
[2]*Pusat Perubatan Universiti Kebangsaan Malaysia*

Abstract

An adrenal mass can be a diagnostic challenge as it is not easy to differentiate the adrenal glands from other adrenal pseudotumours with only radio-imaging. We report a 28-year-old patient who was diagnosed radiologically as an adrenal cortical carcinoma after he presented with abdominal pain and fullness. Biochemically, he demonstrated secondary hyperaldosteronism. Intra-operatively there was a huge mass, inferior to a normal right adrenal, which was histopathologically proven to be a dedifferentiated liposarcoma.

Key words: adrenal pseudotumour, dedifferentiated liposarcoma, histopathology

INTRODUCTION

The investigations of an adrenal mass include assessing its functionality and its potential to be malignant. Often large adrenal tumours (LATs) point to an adrenal cortical carcinoma, especially if patients present with features suggestive of hormonal excess. Preoperative investigations, such as radio-imaging, is integral in establishing a preliminary diagnosis, as well as to provide essential information in formulating a management plan. However, as the adrenals are bordered by various anatomical structures, at times adrenal pseudotumours may be misinterpreted as adrenal pathologies. A large adrenal pseudotumour >4 cm, might be interpreted as an adrenocortical carcinoma if the patient is hypertensive or exhibits hypercortisolism.

CASE

A 28-year-old male who was recently diagnosed as hypertensive for the past 1 year but not on treatment, presented with 1-month history of abdominal pain and fullness associated with nausea, vomiting, and significant weight loss in the preceding three months. Clinical examination revealed blood pressure ranging from 130-140/80-90 mmHg, with presence of a vague mass at the right lumbar region. There were no features suggestive of Cushing's syndrome or phaeochromocytoma. Abdomen ultrasound demonstrated a suprarenal mass measuring 13 cm x 12.5 cm x 14 cm. This was confirmed by a CT scan, which showed a right suprarenal mass, likely of adrenal origin, measuring 14 cm x 12 cm x 15 cm with compression of the inferior vena cava, right renal vein and right renal artery. Biochemically, there was evidence of secondary hyperaldosteronism with raised plasma renin activity and serum aldosterone, possibly due to compression of the renal vasculature by the mass. His serum electrolytes, DHEA-Sulphate, urine catecholamines and steroid profiles were normal (Table 1).

Table 1. Biochemical investigations results of the patient

Parameters	Results	Normal Range
Plasma renin activity	3.08	0.30 – 1.90
Serum aldosterone	325.1	41.71-208.9 pg/ml (supine) 67.40 – 335.1 pg/ml (upright)
DHEA-sulphate	10.44	0.44 – 13.4 µmol/L
24-hour urinary free epinephrine	19	<21 mcg/24 hours
24-hour urinary free norepinephrine	136	15-80 mcg/24 hours
24-hour urinary free dopamine	451	65-400 mcg/24 hours

A month later, he presented with abdominal pain and fullness, suggesting the possibility of an enlarging adrenal mass. Adrenal CT revealed an enlarged mass measuring 15.8 cm x 14.4 cm x 17.9 cm with local infiltration to the right kidney. There were hypodense areas within the tumour, representing areas of necrosis (Figure 1A and 1B).

Due to the rapid progression of the size of the tumour, a right adrenalectomy was performed. However, intraoperatively, a huge peritoneal mass (16 cm x 14 cm x 11cm) was noted inferior to the normal right adrenal gland, with a normal-looking right kidney (i.e., no evidence of tumour invasion). Both the tumour and right adrenal were removed (Figure 2A and 2B).

Histopathological examination of the tumour revealed a FNCLCC (Fédération Nationale des Centres de Lutte Centre Le Cancer) grade 2 dedifferentiated liposarcoma (Figure 3A and 3B). Sections of the tumour show a

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: October 21, 2018. Accepted: January 11, 2019.
Published online first: April 15, 2019.
https://doi.org/10.15605/jafes.034.01.15

Corresponding author: Waye Hann Kang, MD, MRCP (UK)
Lecturer/Endocrinology Trainee
Faculty of Medicine and Health Sciences
University Tunku Abdul Rahman
Sungai Long Campus Jalan Sungai Long
Bandar Sungai Long, Cheras 43000, Kajang, Selangor, Malaysia
Tel. No: +603 9086 0288
Fax No: +603 9019 8868
E-mail: kangwh@utar.edu.my
ORCiD: https://orcid.org/0000-0003-3209-7196

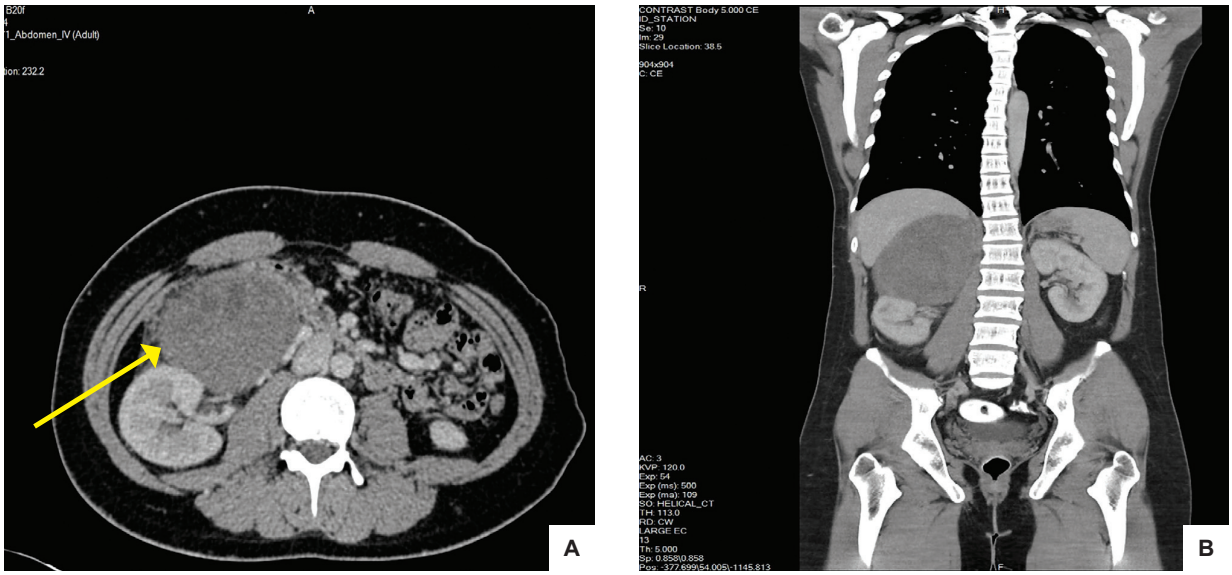

Figure 1. (A) Suprarenal mass with hypodense areas displacing the right kidney postero-inferiorly (CT Abdomen axial view); **(B)** CT Abdomen (coronal view).

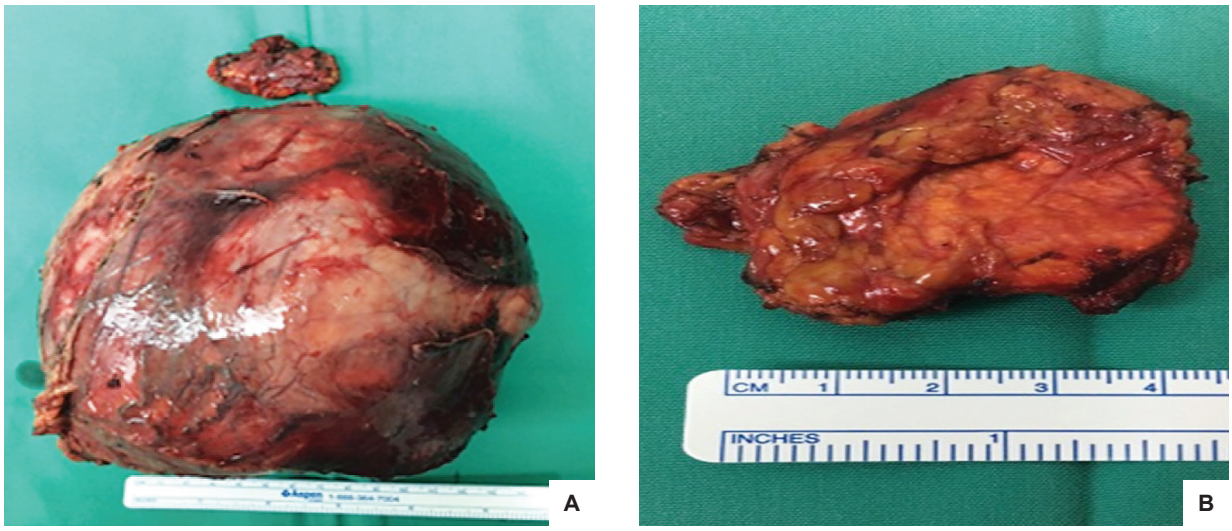

Figure 2. (A) Huge mass measuring 16 cm x 14 cm x 11 cm, weighing 1610.6 g, comparing to the normal right adrenal gland (4.0 cm x 3.5 cm x 1.3 cm); **(B)** Normal right adrenal measuring 4.0 cm x 3.5 cm x 1.3 cm.

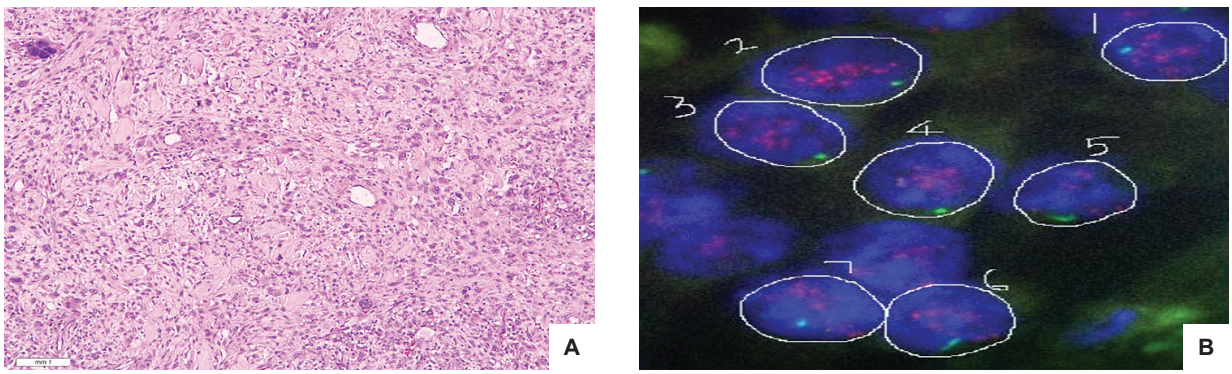

Figure 3. (A) Dedifferentiated area composed of diffuse sheets of pleomorphic cells displaying large irregular nuclei with vesicular chromatin, inconspicuous nucleoli and moderate eosinophilic cytoplasm. Numerous bizarre and multinucleated cells are seen (H&E, x40); **(B)** Fluorescence in situ hybridization (FISH) analysis for MDM2 gene using MDM2/CEP 12 probe (green signal) (VYSIS), shows many nuclei with amplified signals (red signal), i.e., consistent with MDM2 gene amplification.

fairly circumscribed tumour composed of diffuse sheets of pleomorphic cells displaying large irregular nuclei with vesicular chromatin, inconspicuous nucleoli, and moderate pale eosinophilic bubbly cytoplasm with indistinct borders. Numerous bizarre and multinucleated cells are seen with occasional mitoses (mitotic count of 4-5 mitoses/10 hpf). Sheets of atypical adipocytic cells and lipoblasts, were scattered collagen bundles, are seen throughout the high-grade component. There is tumour necrosis (<50%) and presence of a focus of chondroid differentiation.

Fluorescence in-situ hybridization (FISH) analysis for MDM2 gene were performed using Vysis MDM2/CEP 12 probe (Abbott Molecular, USA). There were many nuclei with amplified signals seen, consistent with MDM2 gene amplification.

Sections of the right adrenal gland show normal adrenal tissue. There is a clear demarcation between the tumour and residual adrenal tissue with clear margins from the tumour cells.

Postoperatively, the patient's blood pressure normalised without requiring any anti-hypertensive agents. He was subsequently referred to the oncology team for subsequent management.

DISCUSSION

Large adrenal tumours (LATs), defined as adrenal masses with the size of 6 cm or more, are often rare with the incidence of 8.6% to 38.6%.[1–3] The discovery of a LATs often indicates malignancies unless proven otherwise.[2] A study by Mege et al., in 2014 reported that 64% of their LATs patients had malignancies, with 44%, 27% and 21% of these patients having adrenocortical carcinomas, adrenal metastases and malignant phaeochromocytomas respectively.[4]

However, adrenal pseudotumours can sometimes be misinterpreted as LATS. Kerkhofs et al., identified several adrenal pseudotumours, which include adrenal lymphomas, liposarcomas, schwannomas, ganglioneuromas, haemangioma, angiomyolipoa, epitheliod angiosarcomas, leiomyosarcoma, and adrenal cysts.[5] There have been other reports of an accessory spleen or colon being misinterpreted as pseudotumours. In large tumours >4 cm, it may be difficult or even impossible to differentiate between adrenal tumours and pseudotumours, especially if they show features of hyperfunctional adrenals. If an adrenal mass is highly suspicious to be of malignant origin, then a radical surgical resection is of utmost importance for histopathological confirmation of the pathology.

Retroperitoneal liposarcomas (LPS) can be mistaken for an adrenal mass. Dedifferentiated liposarcomas (DDLPS), commonly found retroperitoneally, are the most frequent subtype, accounting almost 45% of all retroperitoneal soft tissue sarcomas.[6] The DDLPS are believed to often start off with a well-differentiated liposarcomas (WDLPS), usually a non-metastasizing tumour composed of matured adipocytes, which later dedifferentiate and metastasize, evolving into a more aggressive local disease with high metastatic potential.[7]

DDLPS have been proven to exhibit amplification of chromosome 12q13-15, involving the liposarcoma genesis oncogenes MDM2, HMGA2, CDK4.[8,9] The oncogenes MDM2 and CDK4 are responsible for the malignant tumour process.[10] MDM2 is essential for ubiquitination and degradation of the tumour suppressor gene p53; by inhibiting P53, apoptosis is decreased resulting inversely in increased cell survivals.[11,12] CDK4 allows the cell cycle to proceed unregulated by phosphorylating the Rb gene products.[13] On the contrary, amplication of other genes such as ASK1 and JUN results in inactivation of peroxisome proliferator-activated receptor (PPAR) gamma, hence inhibiting adipocytic differentiation in DDPLS.[10]

Histologically, DDLPS is characterized by the abrupt transition from WDLPS to a region of non-lipogenic sarcoma. Under the microscope, the dedifferentiated area appears as atypical non-lipogenic stromal cells with hyperchromatic nuclei scattered in fibrous septa. Ninety percent of DDLS arises de novo, while 10% occurs in recurrence. In recurrent tumours, dedifferentiation occurs in almost 20% of first time recurrences and 44% of second-time local recurrences, implying acquisition of additional aberrations within WDLS as it recurs.[14]

The risk of dedifferentiation is higher in deep-seated tumours, especially in the retroperitoneum and is probably a time-dependent phenomenon.[10]

Often, DDLS can be diagnosed easily through adrenal radio-imaging such as CT or MRI, with features often described as heterogenous, non-lipogenic with a region of abnormal-appearing fat.[15] In cases where histological examination is equivocal, immunohistochemical staining of MDM2 (sensitivity 95%, specificity 81%) and CDK4 (sensitivity 92%, specificity 95%), allows a definitive diagnosis of DDLPS.[16] The detection of MDM2 amplification and overexpression of MDM2 genes (100% of cases) and CDK4 (90% of cases) using FISH or quantitative PCR is highly specific for the diagnosis of DDLS.[10]

Treatment of primary retroperitoneal DDLS is surgery. Systemic therapy with chemotherapy or targeted agents should be considered if a surgical margin is not feasible or there is recurrence. Targeted therapies aimed at MDM2 and CDK4 oncogenes are still in clinical trials.[6] Prognosis is determined by local recurrences (40-60%), especially in the retroperitoneum, despite the low metastatic potential (15-20%). There is an overall rate of 41% of local recurrence. The overall mortality ranges from 28-40% at 5 years.[10,15] Retroperitoneal lesions have 100% local recurrence rate and almost invariably lead to death.

CONCLUSION

Presentation of an adrenal mass can pose a diagnostic challenge as it is difficult to differentiate an adrenal mass from other retroperitoneal masses (lymphomas, liposarcomas, ganglioneuromas, etc.) by using radio-imaging modalities due to the close proximities of various organs in a tight retroperitoneal space. Surgical resection is often necessary if the mass exhibits features suggestive of malignancy while a histopathological examination will provide a definite diagnosis. Retroperitoneal liposarcomas are often aggressive and may present to the endocrinologist

as an adrenocortical carcinoma. Identification of the MDM2 and CDK4 genes via immunohistochemical staining, qualitative PCR and FISH is diagnostic.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References

1. Parnaby CN, Chong PS, Chisholm L, Farrow J, Connell JM, O'Dwyer PJ. The role of laparoscopic adrenalectomy for adrenal tumours of 6 cm or greater. Surg Endosc. 2008;22(3):617-21. PMID: 18071798. https://doi.org/10.1007/s00464-007-9709-7.
2. Liao CH, Chueh SC, Lai MK, Hsiao PJ, Chen J. Laparoscopic adrenalectomy for potentially malignant adrenal tumors greater than 5 centimeters. J Clin Endocrinol Metab. 2006;91(8):3080-3. PMID: 16720665. https://doi.org/10.1210/jc.2005-2420.
3. Zografos GN, Farfaras A, Vasiliadis G, et al. Laparoscopic resection of large adrenal tumors. JSLS. 2010;14(3):364-8. PMID: 21333189. PMCID: PMC3041032.https://doi.org/10.4293/108680810X12924466007160.
4. Mege D, Taieb D, Lowery A, et al. Contemporary review of large adrenal tumors in a tertiary referral center. Anticancer Res. 2014;34(5):2581-8. PMID: 24778080.
5. Kerkhofs TM, Roumen RM, Demeyere TB, van der Linden AN, Haak HR. Adrenal tumors with unexpected outcome: A review of the literature. Int J Endocrinol. 2015;2015:710514. PMID: 25883649. PMCID: PMC4389822. https://doi.org/10.1155/2015/710514.
6. Crago AM, Singer S. Clinical and molecular approaches to well-differentiated and dedifferentiated liposarcoma. Curr Opin Oncol. 2011;23(4):373-8. PMID: 21552124. PMCID: PMC3253354. https://doi.org/10.1097/CCO.0b013e32834796e6.
7. Dalal KM, Kattan MW, Antonescu CR, Brennan MF, Singer S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann Surg. 2006;244(3):381-91. PMID: 16926564. PMCID: PMC1856537. https://doi.org/10.1097/01.sla.0000234795.98607.00.
8. Fletcher CD, Akerman M, Dal Cin P, et al. Correlation between clinicopathological features and karyotype in lipomatous tumors. A report of 178 cases from the Chromosomes and Morphology (CHAMP) Collaborative Study Group. Am J Pathol. 1996;148(2):623-30. PMID: 8579124. PMCID: PMC1861666.
9. Meis-Kindblom J, Sjögren H, Kindblom LG, et al. Cytogenetic and molecular genetic analyses of liposarcoma and its soft tissue simulators: Recognition of new variants and differential diagnosis. Virchows Arch. 2001;439(2):141-51. PMID: 11561754. https://doi.org/10.1007/s004280100423.
10. Coindre JM, Pédeutour F, Aurias A. Well-differentiated and dedifferentiated liposarcomas. Virchows Arch. 2010;456(2):167-79. PMID: 19688222. https://doi.org/ 10.1007/s00428-009-0815-x.
11. Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. Amplification of a gene encoding a p53-associated protein in human sarcomas. Nature. 1992;358(6381):80-3. PMID: 1614537. https://doi.org/10.1038/358080a0.
12. Oliner JD, Pietenpol JA, Thiagalingam S, Gyuris J, Kinzler KW, Vogelstein B. Oncoprotein MDM2 conceals the activation domain of tumour suppressor p53. Nature. 1993;362(6423):857-60. PMID: 8479525. https://doi.org/10.1038/362857a0.
13. Ortega S, Malumbres M, Barbacid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochim Biophys Acta. 2002;1602(1):73-87. PMID: 11960696. https://doi.org/10.1016/S0304-419X(02)00037-9.
14. Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg. 2003;238(3):358-70. PMID: 14501502. PMCID: PMC1422708. https://doi.org/ 10.1097/01.sla.0000086542.11899.38.
15. Murphey MD, Arcara LK, Fanburg-Smith J. From the archives of the AFIP: Imaging of musculoskeletal liposarcoma with radiologic-pathologic correlation. Radiographics. 2005;25(5):1371-95. PMID: 16160117. https://doi.org/10.1148/rg.255055106.
16. Binh MBN, Sastre-Garau X, Guillou L, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: A comparative analysis of 559 soft tissue neoplasms with genetic data. 2005;29(10):1340-7. PMID: 16160477.