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Mixed corticomedullary adrenal carcinoma – case report: Comparison in features, treatment and prognosis with the other two reported cases

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ABSTRACT

INTRODUCTION: Adrenal corticomedullary adenoma was reviewed in many cases in PubMed Library, While the coincidence corticomedullary adrenal carcinoma in the same gland was just described in two cases in the medical literature. Our case is the third to be reported and was treated with surgery and adjuvant chemotherapy and followed for two years.

PRESENTATION OF CASE: A 50-year-old man suffered from a mass effect in the left abdominal side. While the laboratory showed a mild elevation in the levels of both serum cortisol and 24 h urine cortisol, radiological images were highly suggested an adrenal malignant tumor without metastasis. At surgery a 22 cm sized mass was completely resected. Immunohistochemical study identified expression of both adrenocortical carcinoma and pheochromocytoma markers.

DISCUSSION: Cases of coincidence corticomedullary tumor have been published in many reviews, cortical and/or medulllary hypersecretion were not always detected preoperatively by biochemical tests.

Mixed corticomedullary carcinoma are exceedingly rare, we came across three reported cases in medical literature, in one case laboratory tests confirmed both cortical and medulla hypersecretion, while the two others detected only cortical hypersecretion. The final diagnosis was always confirmed by immunohistochemical staining.

CONCLUSION: It could be noted that this is the first comparison of presentation, diagnosis, treatments and follow-up of the three cases of Mixed corticomedullary carcinoma. This could contribute to understanding the behavior and management of this rare malignancy and make it more familiar in clinical practice.

1. Introduction

Adrenocortical carcinoma (ACC) is a rare malignancy (1–2 per 1 million per year in adults) with a heterogeneous presentation and a variable but generally poor prognosis [1]. 40% of this malignancy is a nonfunctional lesion at presentation [2]. Pheochromocytoma, the adrenal-medulla neoplasm, is also rare (2–8 cases per million per year) [3] and 13% of patients with adrenal pheochromocytoma usually have normal blood pressure [4]. All these extremely uncommon findings exist in a single gland we are reporting here. Beside the case that was presented as a summary by the European Congress of Endocrinology [5] in 2008, two other mixed corticomedullary carcinoma cases were reported with full details [6,7].

2. Case presentation

A 50-year-old man was referred to our clinic with a chronic story of abdominal pain in his left flank, anorexia, weakness and significant weight loss during last six months. The patient denied other gastrointestinal symptoms, fever, night sweats, headaches, palpitations, dizziness, blurred vision, chest pain, shortness of breath, panic attacks, decreased libido and hair or skin changes. The past medical and surgical history was unremarkable. There was a family history of type 2 diabetes mellitus and hypertension. The patient was a heavy smoker and he gave up drinking alcohol three years ago. He was 165 cm tall, weighed 65 kg, with BMI of 23.8 kg/m^2. He had lost 25 kg per the past six month. A full physical exam showed vital signs within normal limited: blood pressure, 130/85 mmHg;

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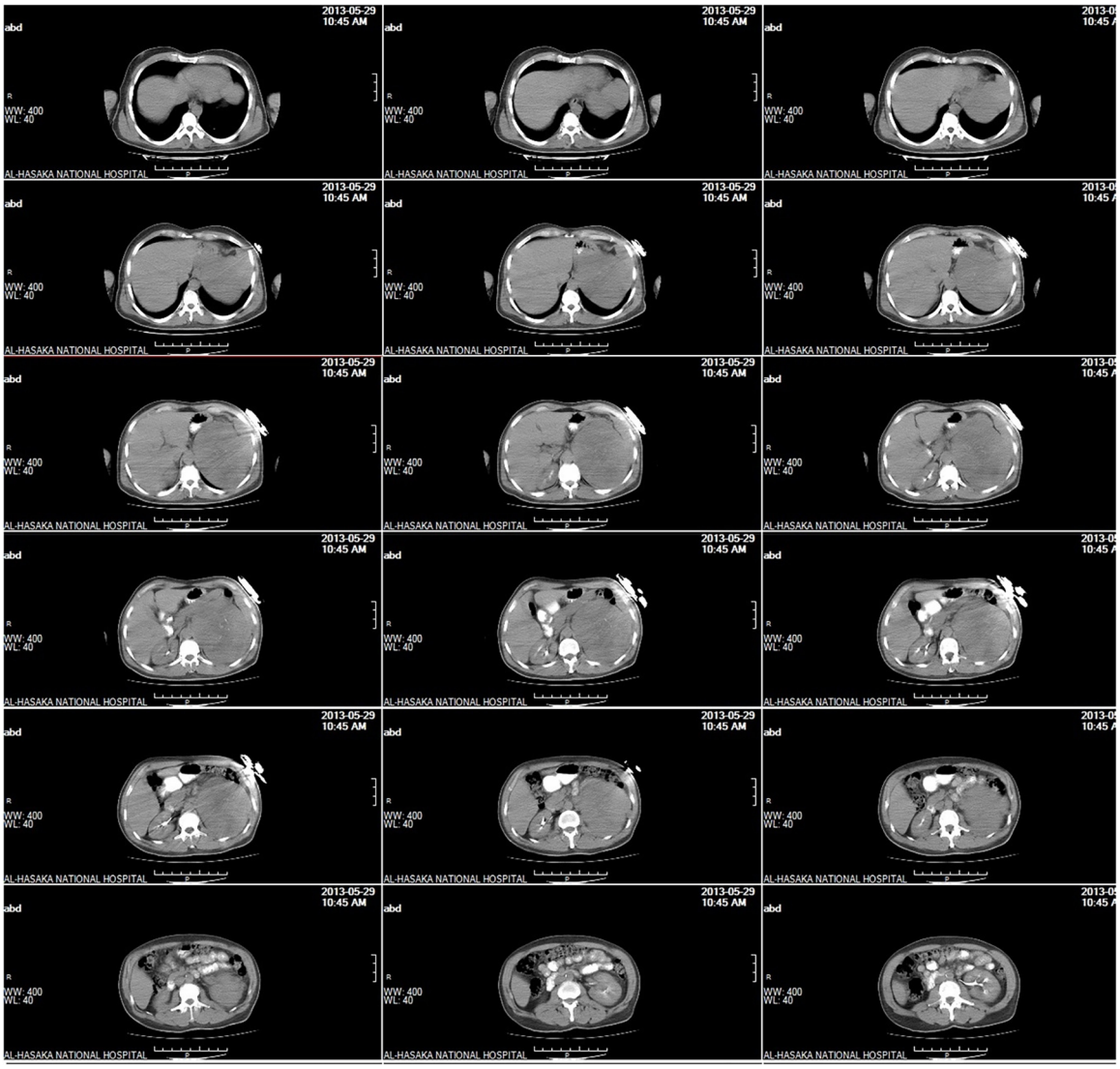

Fig. 1. Abdomen CT scan at initial diagnosis. A 20 cm sized mass in the left upper quarter with irregular margin and inhomogeneous appearance.

pulse rate, 95 beats/min; with no changing in the erect position. The respiratory rate was 20/min; temperature, 37.3 °C; and oxygen saturation, 99% while breathing room air. A palpable solid mass was found in the left upper abdominal quadrant. Initial laboratory workup demonstrated the following values: hemoglobin, 8.8 g/dL (reference range, 12.0–16.0 g/dL); potassium, 4.2 mEq/L (reference range, 3.5–5.2 mEq/L); fasting blood glucose, 71 mg/dL (reference range, 66–99 mg/dL); creatinine, 1.09 mg/dL (reference range, 0.7–1.5 mg/dL); ALP, 60 U/L (reference range, up to 300 U/L), among other findings were within normal limits. Abdominal CT indicated an adrenal lesion in the left upper quarter that displaced left kidney, spleen and pancreas [Fig. 1]. Its size (approximately 20 cm), irregular margin and heterogeneous appearance suggested malignancy.

The patient was admitted for monitoring and further study. No paroxysmal attack occurred during the collection period: neither episodic nor sustained hypertension was recorded, blood glucose numbers remained within normal range, and electrocardiogram was normal. His free cortisol in 24 h urine, 151.28 ug/24 h (reference range, 36–137 ug/24 h); 8-AM serum cortisol level, 24.34 ug/dL (reference range, 6.2–19.4 ug/dL); ACTH < 1.00 pg/ml (reference range, 7.2–63.3 pg/ml) and vanillylmandelic acid in 24 h, 4.3 mg/24 h (n = 1.9 9.8).

Left modified Makuuchi incision was made for an exploratory laparotomy. The adrenal mass was identifed [Fig. 2]. It did not grossly involve the left kidney, renal vessels, pancreas or major retroperitoneal vessels, but the mass vessels were very difficult to be separated from the lower portion of spleen. The en-bloc resection of the mass was performed and the left adrenal with spleen were resected completely.

Grossly, the tumor was well defined and encapsulated, solid, yellowish gray with a little fat and focally rimmed with normal adrenal tissue. The tumor weighted 2100 g and measured 22 cm in maximum dimension. Microscopically sections revealed an undifferentiated high grade carcinoma with frank malignant features and evident tumor necrosis. Many of the cells were large, pleomorphic, some were multinucleated and bizarre with frequent mitoses up to 4/hpf [Fig. 3A] with aberrant forms [Fig. 3B]. Average mitotic figures were 60 in 50/hpf. The cells were arranged in sheets with only occasional cells with clear cytoplasm. Focal vascular invasion was seen, but no capsular invasion was identified. This was in keeping with weiss score 7. Margins of the resection were free. Immunohistochemically, the neoplastic cells were positive for inhibin and calretinin markers. ChromograninA was also positive with focal perinuclear Golgi pattern. Chromogranin Golgi pattern had been desribed in neuroendocrine tumor. S-100 protien marker

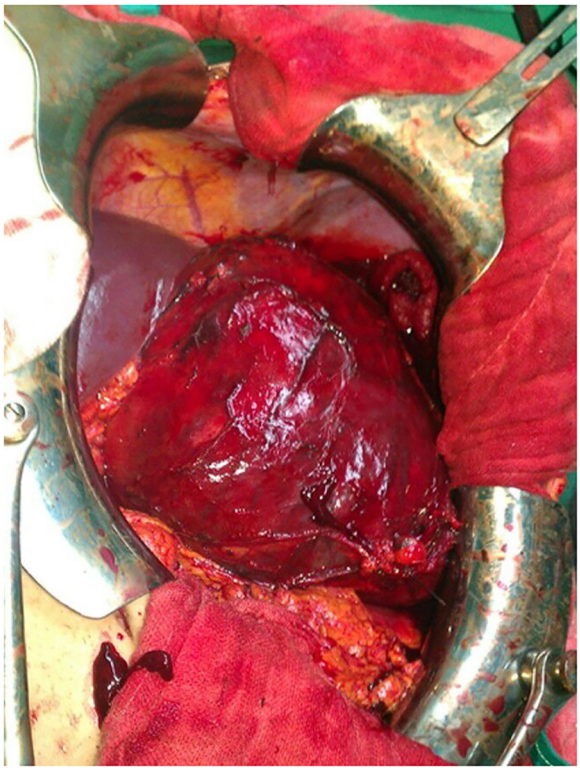

Fig. 2. The adrenal mass in the abdominal cavity.

was expressed in many sustenticular cells [Fig. 4A–F]. This panel identifies mixture of both cortical carcinoma and medullary neoplastic cells (pheochromocytoma). The pathological study of the spleen was negative for neoplastic changes.

The patient was discharged from the hospital seven days later with no surgical complications. He was referred to oncology department. Eventhough mitotane is one of the best choice, it wasn't available in Syria, so a dose of etopside (D1–D3) with carboplatine

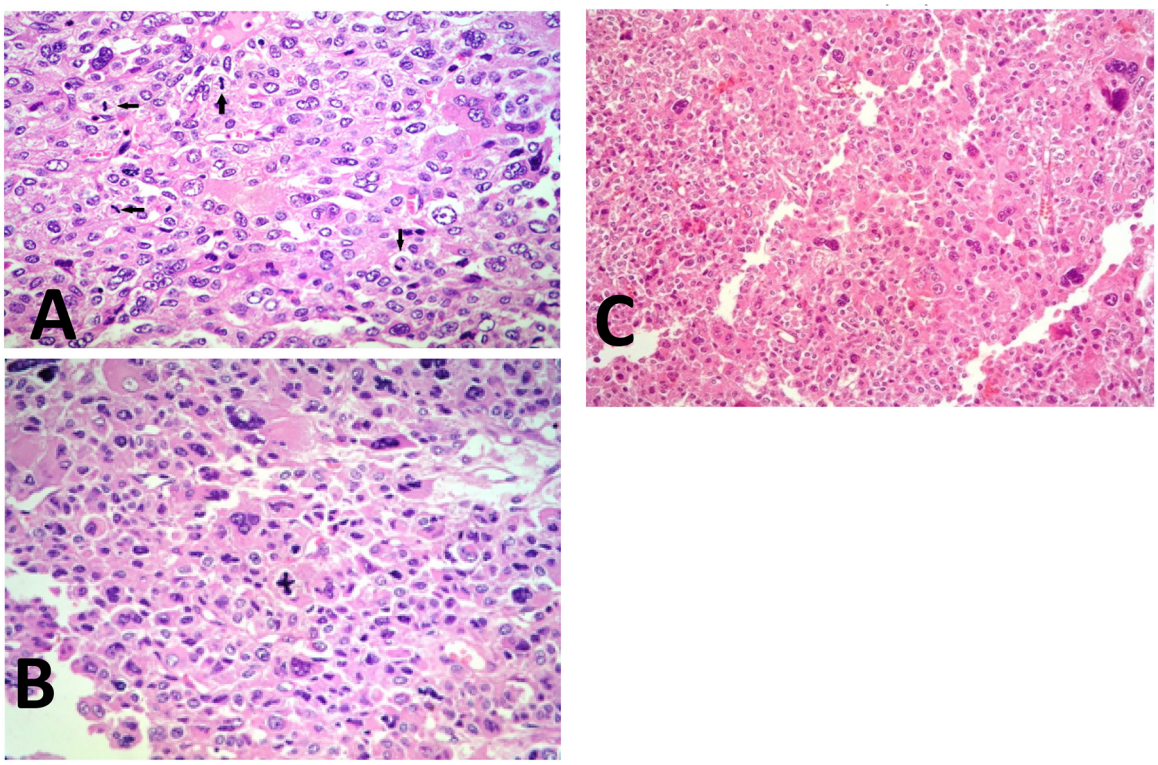

Fig. 3. H&E A. Four mitosis in this field marked with arrows three in metaphase and one in anaphase. B. Atypical mitosis is seen in the center of the field. C. Tumor necrosis is displayed in this field.

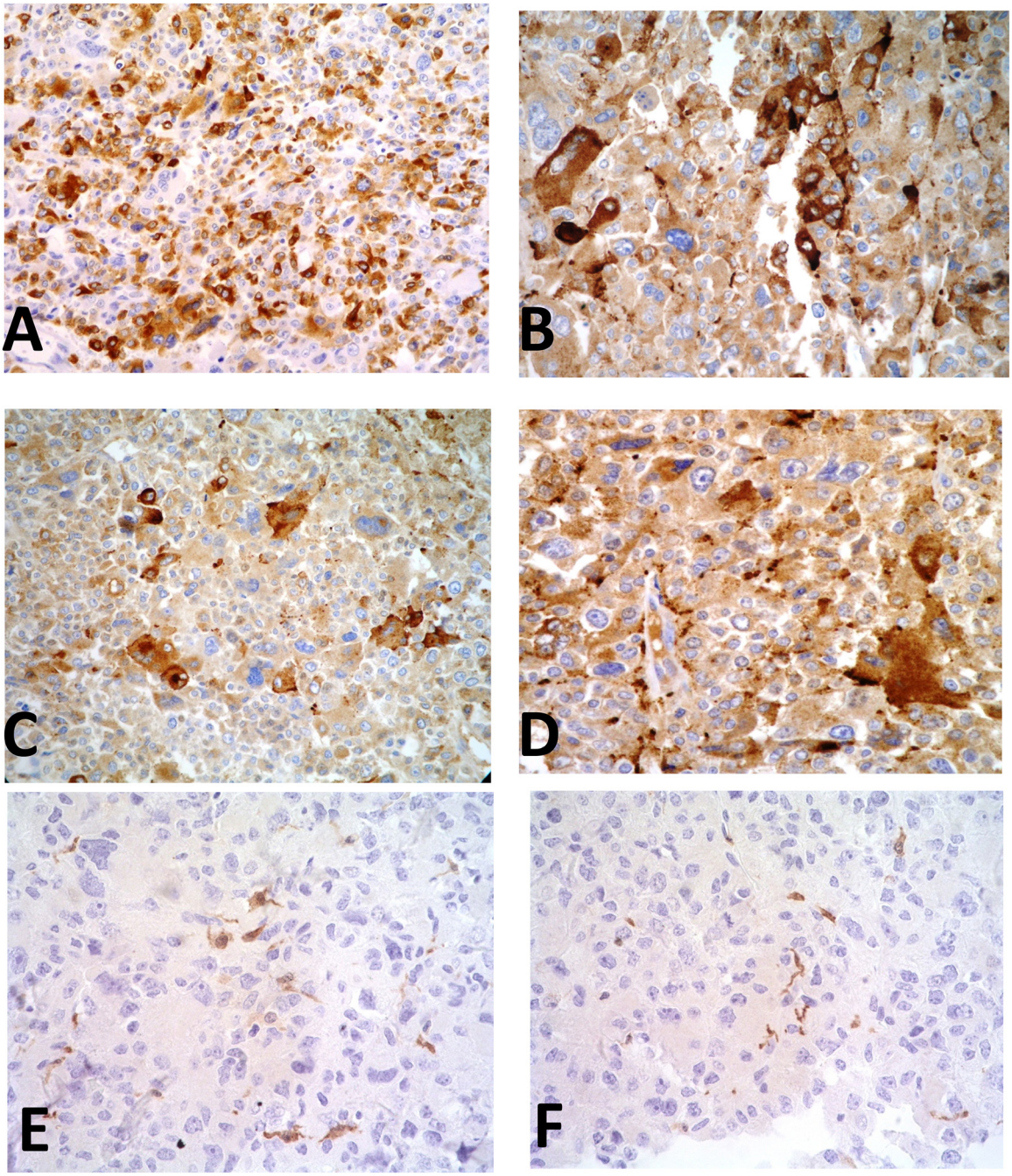

Fig. 4. Results of the immunohistochemical studies: A – Inhibin marker is positive. B – ChromograninA marker. Some tumor cells stain darkly. C – ChromograninA marker showing a Golji pattern. D – Claretinin marker is positive. E+F – S-100 protein immunostain mark sustenticular cells.

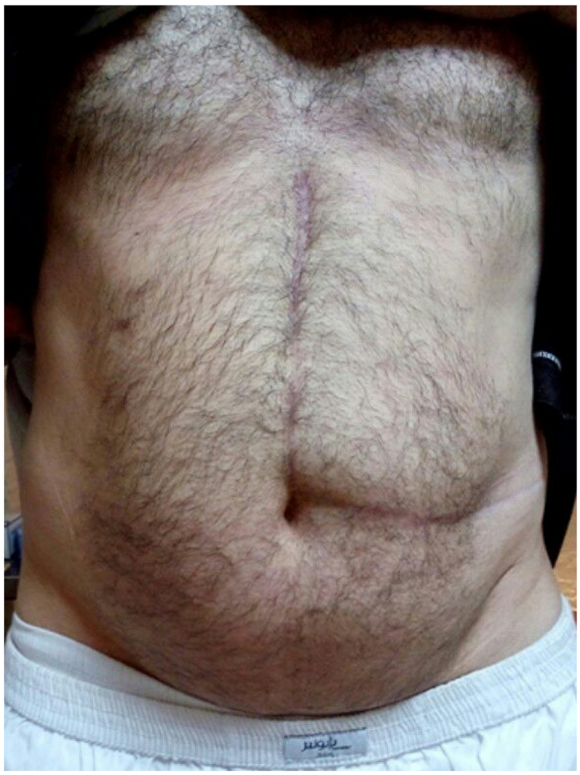

Fig. 5. The patient in 8 months after the surgery.

(D1) every 3 weeks were administered and a total of nine doses was given. Total blood cells, BUN and creatinine were monitered as an outpatient. The patient came back eight months post-surgery for follow up.

He gained 20 kg weigh [Fig. 5], his new BMI was 31.2 kg/m^2, none of old symptoms was back, and no new complains were recorded. Laboratory tests were normal. A chest and Abdomen CT appeared no specific changes, and no evidence of metastasis [Fig. 6].

One year later, the patient complainted of recurrent symptoms of fatigue and weight loss. Screening CT showed two irregular masses: one was (5.5 × 8 cm^2) posterior to the stomach, the other was (16 × 17 cm^2) in the right lobe of the liver [Fig. 7]. Six cycles of cyclophosphamide, doxorubicin and vincristine were given.

3. Discussion

Adrenocortical carcinoma (ACC) is a rare malignancy (1–2 per 1 million per year in adults) [1], and 40% of them is a nonfunctional lesion at presentation [2]. Pheochromocytoma is also rare, and 13% of patients with adrenal pheochromocytoma come with normal blood pressure [4]. Cases of coincidence corticomedullary tumor were published and compared in many reviews [6–8,14]. Michalopoulos et al. [7] described 15 cases of coexisted of pheochromocytoma with cortical adenoma, It is remarkable that in only 6/15 cases [9–13], both cortical and medullary hypersecretion were confirmed preoperatively by biochemical exams. Also, Alexandraki et al. [14] reported 16 cases of corticomedullary mixed adrenal tumor, in three of these 16 cases [14–16], neither cortical nor medullary hypersecretion was detected preoperatively by biochemical tests, and the diagnosis was made postoperatively by histoimmunostains.

Mixed corticomedullary carcinoma was detected just three times in medical literature. One case was a summary in The European Congress of Endocrinology [5] in 2008, and the other two cases were reported in 2012–2013 with full details [6,7]. In [Table 1] we

Table 1
Review of the three documented cases that report "mixed corticomedullary carcinoma in the same gland".

Case	Sex/age	Size/Site		Clinical presentation	Abnormal Laboratory	Metastasis at presentation	Treatment	Immunohistochemically	Adjuvant chemotherapy	Follow-up in:	Radiology	Laboratory
[6] 2012	F/78	10 cm.	Left	Dizziness, hypertension with new hypertensive episodes; weight loss.	Serum dehydroepiandrosterone: 571 mg/dL (n < 200). Urinary metanephrines: 457 μg/24 h (52–310 mg/24 h)	No evidence.	Adrenalectomy	Immunohistochemical staining for chromogranin A, synaptophysin, melan-A, and inhibin was positive. S-100 staining highlights sustentacular cells	Not performed until the metastasis had been discovered; carboplatin and etoposide.	121 days	8.5 cm sized mass adjacent to the adrenalecto-my site. Liver mass measuring 1.7 cm	Plasma normetanephrine 190 pg/mL (n = 0–145).
[7] 2013	M/63	8 cm.	Right	Mass effect, abdominal pain; Weight loss.	Morning cortisol: 661 nmol/L (n = 171–536). Urine Catecholamines: 150 μg/24 h (10–280) NSE (ng/mL): 20.33 (<12.5) Chromogranin A: 21 ng/mL (n = 2–18). Morning cortisol after 1 mg overnight dexamethasone suppression test: 100 nmol/l (n < 50).	No evidence.	Adrenalectomy	The neoplastic cells were positive for chromogranin A, synaptophysin, NSE, vimentin and S-100. And were focally positive for calretinin and CKAE1/AE3.	Six cycles of etoposide and cisplatin. No additional chemotherapy was offered After the metastasis were confirmed.	Radiology and laboratory follow-up in 1 year. Then the patient died 18 months after the operation: (respiratory failure due to diffuse pulmonary metastases).	CT scan revealed small liver and lung metastases.	Morning cortisol: 830 nmol/lt (n = 140–690). ChromograninA: 415 ng/mL (n = 2–18). Urine Catecholamine's: 3021 μg/24 h (n = 10–280).
Our case 2016	M/50	22 cm. Left		Mass effect, abdominal pain; weight loss.	Morning cortisol: 24.34 ug/dL (n = 6.2–19.4). Urine free cortisol: 151.28 ug/24 h (n = 36–137). ACTH < 1.00 pg/ml (n = 7.2–63.3). Vanillylmandelic acid in 24 h urine: 4.3 mg/24 h (n = 1.9–9.8).	No evidence.	in Adrenalectomy	Immunohistochemical staining for inhibin, calretinin, chromogranin A and S-100 markers are positive. MelanA marker is negative	A dose of etoposide and carboplatin every 21 days. (six cycles)	8 months 18 months after the operation Six months later	No evidence of metastasis A regional mass (5.5*8 cm^2); A liver metastasis (16*17 cm^2): Six cycles of cyclophosphamide, doxorubicin & vincristine + lung metastases.	Vanillylmandelic acid in 24 h urine: 7.21 mg/24 h (n = up to 8.0).

Abbreviation: ACC: adrenocortical carcinoma. n: normal range. NSE: neuron-specific enolase.

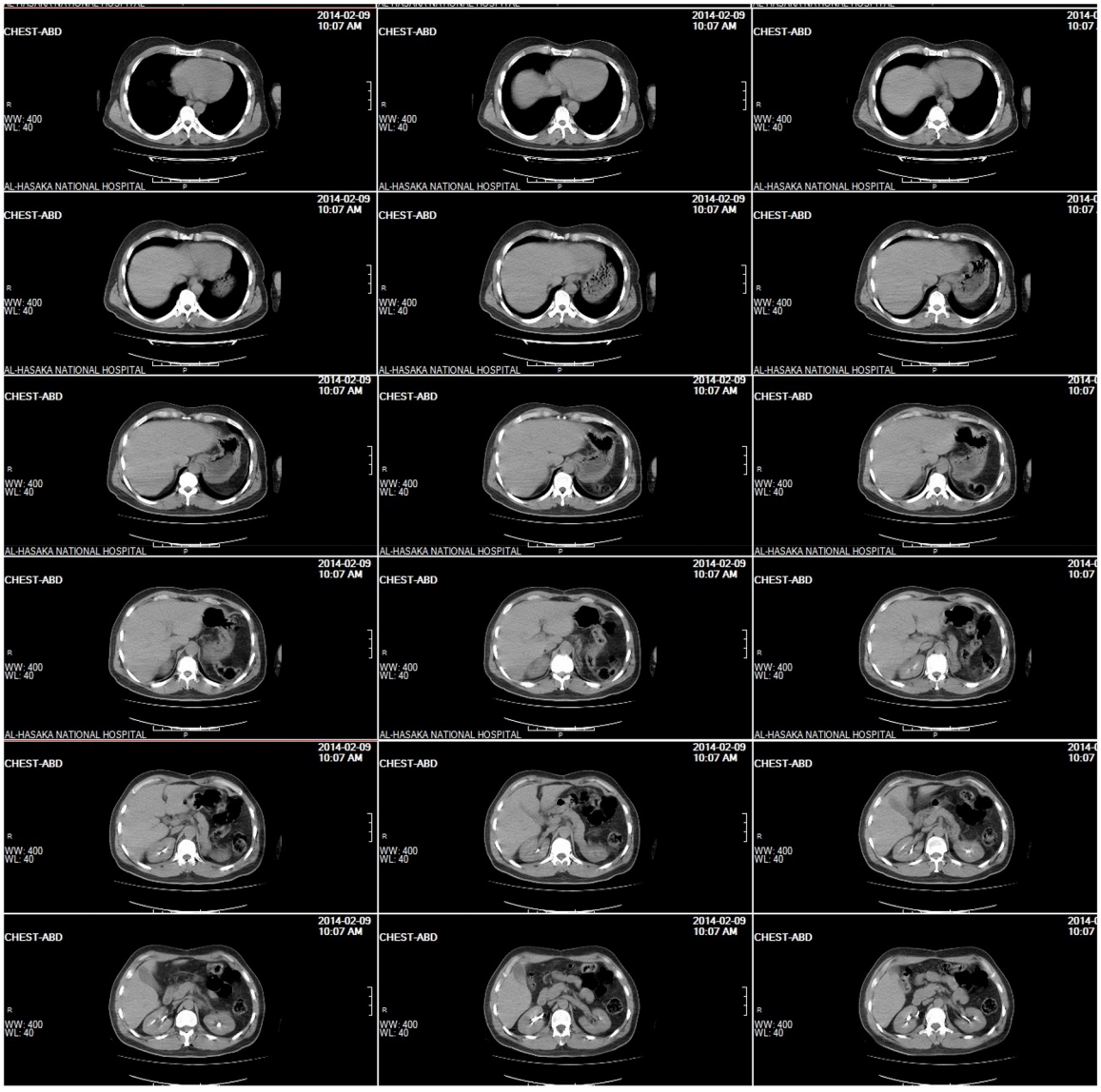

Fig. 6. Chest and abdomen CT scan 8 months after left ardrenalectomy and splenectomy. There was no specific changes, and no evidence of metastasis.

compared the three full-details cases; the current one with the 2012–2013 cases, we found that one case presented with hypertensive episodes, the two others described only the mass effect. At presentation, all masses were suggestive of malignancy by imaging study, as the mean tumor size of adrenal cortical carcinoma is 11.5 ± 4.7 cm [17]. Preoperatively, the laboratory tests in one case confirmed cortical and medullar hypersecretion, the two others confirmed only cortical hypersecretion. All three authors avoided the laparoscopic procedure and reminded to respect the principles of radical oncological surgery [7]. The immunohistochemical staining came to confirm the corticomedullary adrenal carcinoma by either inhibin, calretinin or both, chromograninA and S-100. The chemotherapy was administered as we described in [Table 1], and the prognosis was definitely bad, furthermore it was worse than the adrenal cortical carcinoma as Michalopoulos et al. believed, and the median survival was also less than that in adrenal cortical carcinoma [7].

4. Conclusion

In this report, we describe the diagnosis, treatment plan and close follow-up of a 50-year-old man with a 22 cm sized left adrenal corticomedullary carcinoma. The review, we made, of the three published cases make the behavior and management of this rare malignancy, more familiar in clinical practice.

Conflicts of interest

There is no conflict of interest.

Sources of funding

No sources of funding.

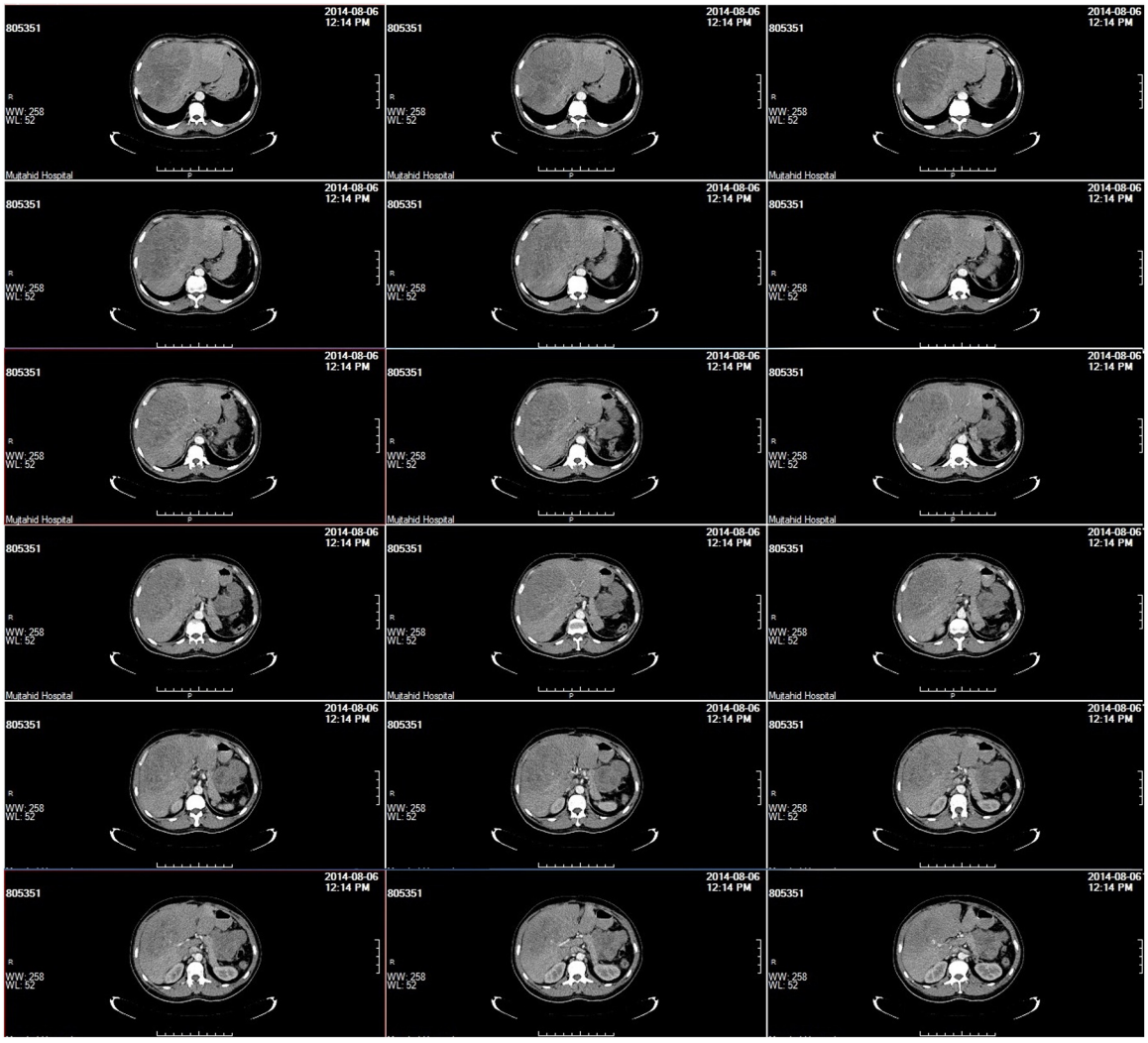

Fig. 7. Screening CT scan 18 months after the surgery. Two irregular masses: one posterior the stomach ($5.5 \times 8\,cm^2$), the other in the right lobe of the liver ($16 \times 17\,cm^2$).

Ethical approval

Our manuscript is a case report not a research.

Consent

The consent was obtained from the patient for medical publishing purposes, all the information including images. A copy of the written consent is available for review by the editors of this journal. We report our case in the form of SCARE guidelines and its 14-items checklist [18].

Author contribution

Mhd Belal Alsabek: corresponding author, collected the data, reviewed the PubMed Library and wrote the paper. Riad Alhumaidi: the surgeon who prepared the patient and run the operation. Bader Ghazzawi: a member of the pathologist team. Ghiath Hamed: a member of the pathologist team. Alhadi Alseoudi: the chemotherapist.

Guarantor

Bader Ghazzawi; Ghiath Hamed.

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