

Oncology

Malignant pheochromocytoma with negative biochemical markers: Is it time to reclassify pheochromocytomas?



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ARTICLE INFO

Keywords:

Pheochromocytoma
Adrenal
Catecholamines
Hypertension

ABSTRACT

Pheochromocytomas are catecholamine producing tumors of adrenal gland generally diagnosed by presence of these markers in urine or plasma. However, a few may be marker-negative and challenging for clinicians. Several reports of these marker-negative pheochromocytomas may warrant necessity for a new classification of these tumors. Adrenergic blockade before surgery is one of the main reasons for recognition of these cases. We present a case of marker-negative pheochromocytoma which turned out to be malignant on its recurrence. To our knowledge, this is the only case of malignant marker-negative pheochromocytoma reported in literature so far.

Introduction

Pheochromocytomas are tumors of adrenal medulla usually secreting catecholamines or their metabolites. Diagnosis is usually confirmed by presence of these markers in urine or plasma. At least 10% of pheochromocytomas are malignant. Usual treatment for pheochromocytomas includes complete surgical resection of the tumor with pre-operative alpha-blockade. Although most tumors are secretory in origin, rarely they are biochemically silent, which makes both diagnosis and treatment challenging.¹

We present, to our knowledge, the only case of biochemically negative but malignant pheochromocytoma so far.

Case presentation

39-year-old female presented with right flank pain accompanied by intermittent headaches, palpitations and sweating for 3 months. Blood pressure at the admission was 190/105 mmHg with pulse of 88 beats/min. Ultrasonography revealed a 60 * 30 mm solid mass in the right suprarenal region. MRI was done which revealed a 58*40*38 mm heterogeneous tumor in the right adrenal gland, containing fatty tissues, with further enhancement of its solid regions [Fig. 1]. Laboratory tests including serum creatinin, electrolytes, aldosterone and plasma renin activity were normal. 24-hour urinary fractionated

metanephrines, normetanephrines, vanillylmandelic acid (VMA) and cortisol were also normal. Despite the normal levels of catecholamines, pheochromocytoma remained the most probable diagnosis based on clinical grounds. Surgery was planned and patient received phenox- ybenzamine in combination with propranolol to control tachycardia, hypertension and also for adrenergic-blockade prior to surgery. With subcostal retroperitoneal approach, excision of tumor in the right adrenal region was performed. Microscopic examination confirmed the diagnosis of pheochromocytoma. Some foci of necrosis were also reported. Postoperative period was uneventful.

Unfortunately patient missed the follow-up appointments and was re-admitted 10 months later with the previous same combination of symptoms.

On examination she had blood pressure of 190/110 mmHg. Previous set of laboratory investigations including urinary fractionated metanephrines, normetanephrines and VMA were obtained and were all normal. Additionally 24-h urinary dopamine level was obtained which was also normal. The only remarkable lab studies were serum FBS = 140 mg/dl, HGB = 17,1 g/dl, LDH = 955 U/L and ESR = 65 mm.

Abdominal CT revealed a 95 * 65 mm soft tissue tumor located cephalad and another 55 * 40 mm tumor located posterior-inferior to the right kidney with homogeneous enhancement [Fig. 2]. Malignant pheochromocytoma was suspected and brain MRI, Chest CT and

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<https://doi.org/10.1016/j.eucr.2019.100858>

Received 5 February 2019; Received in revised form 25 February 2019; Accepted 26 February 2019

Available online 05 March 2019

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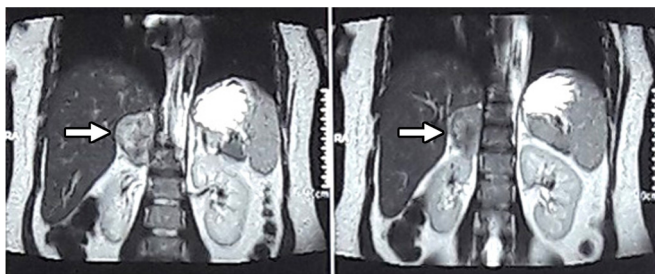


Fig. 1. Abdominal MRI (coronal view) showing right adrenal tumor with heterogeneous signal and enhancement of its solid regions.

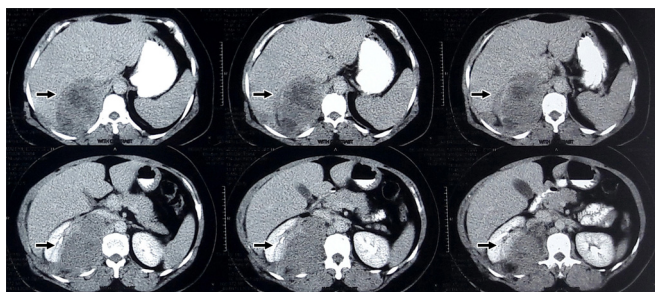


Fig. 2. Abdominal CT (axial view) showing recurrence of tumor cephalad to the right kidney with homogeneous enhancement and displacement of the right kidney and IVC.

Metaiodobenzylguanidine (MIBG) scan were done, all of which were unremarkable. After proper control of hypertension and alpha-blockade, surgery was planned. Using midline transperitoneal approach, retroperitoneal space was explored which revealed multiple tumors in the upper and lower poles of the right kidney with adhesions to the kidney and abdominal wall. Considering probable malignant diagnosis and dense adherence, radical nephrectomy was performed along with careful excision of tumor from abdominal wall. Post operative period was uneventful and blood pressure was normalized. Pathological report confirmed “malignant pheochromocytoma” with extensive foci of necrosis, vascular, capsular and abdominal wall invasions. Immunohistochemistry (IHC) study was positive for synaptophysin and S-100 markers, and negative for cytokeratins, further affirming diagnosis of pheochromocytoma.

Discussion

Malignant pheochromocytoma is a rare entity, comprising 10% of all pheochromocytomas. Negative markers in pheochromocytoma are also very rare. That's why we believe that our case is a “rare in rarity”. Pathology alone is not enough for confirmation of malignant disease. Recurrence, metastasis or local invasion are generally considered as malignant forms of the disease.²

Diagnosis of pheochromocytoma is usually straightforward in patients with typical presentation and positive markers. Measurement of plasma metanephrines or 24-h urinary metanephrines are the gold standard of diagnosis.³

However, about 9% of patients may have normal markers.⁴ Many terms have been used for pheochromocytomas with negative markers, such as biochemically silent, non-functioning, non-secreting, etc. We think that classification for pheochromocytomas should be revised and suggest the term “subchemical pheochromocytoma” for subgroup of patients without any biochemical marker elevations, and “subclinical pheochromocytoma” for subgroup of patients without any obvious symptoms. The latter are usually patients diagnosed with incidentalomas.

Several theories have been proposed for normal levels of markers in

these patients, including: 1) episodically secreting tumors 2) release of small amounts of unmetabolised catecholamines due to rapid intratumoral turnover rate 3) small amount of functioning tissue 4) hemodilution 5) dopamine producing tumors 6) extensive necrosis or hemorrhage 7) small size of the tumor, etc.^{2,4}

Interesting issue about our patient is completely negative markers even after apparently symptomatic, malignant and more aggressive disease recurrence.

In the paper of Lenders et al.⁵ only 2 of 76 patients with hereditary pheochromocytoma and 1 of 138 patients with sporadic pheochromocytoma had normal levels of free metanephrines, all patients being completely asymptomatic and normotensive.

Furthermore, almost all the subchemical cases in literature are benign.² Heavner et al.⁴ observed that none of marker-negative pheochromocytomas were malignant or extra-adrenal in origin. To our knowledge, our patient is the only case of malignant pheochromocytoma with negative biochemical markers in the literature so far. Poudyal et al.³ reported a case of pheochromocytoma with negative markers, which they thought is malignant due to inferior vena cava thrombosis, but didn't have any malignant manifestations in histopathological specimens or further follow-ups.

The largest study comparing marker-negative and marker-positive patients⁴ showed that the most common symptom in marker-positive patients was sustained hypertension (49%), versus abdominal/flank pain (57%) in marker-negative patients. Given high prevalence of vertigo/dizziness among marker-negative patients (29% vs. 3%), authors have called for increased clinical suspicion in patients presenting with these symptoms. Kota et al.² described a case of adrenal incidentaloma with normal metanephrines who developed hypertensive crisis during surgery, and inevitably, surgery was done 2 weeks later after proper alpha-blockade. That's why we want to emphasize on importance of diagnosing subchemical cases of pheochromocytoma, especially due to indisputable role of pretreatment with alpha-blockers in reducing mortality associated with surgery.

Conclusion

Marker-negative pheochromocytomas are rare form of the disease. Malignant pheochromocytomas are even more critical form and usually secrete metabolites. However a physician must always be aware of patients with negative markers who present with typical symptoms, and must use combination of clinical, radiologic and biochemical studies for diagnosis. This is especially crucial when choosing patients for pre-surgical alpha-blockade.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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