Spontaneous resolution of a patient with a symptomatic pheochromocytoma

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Data sharing statement

Access to the data can be obtained through the authors.

Ethical considerations

Ethics approval was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (ref. no. 688/2023) on the 17 January 2024. Informed consent was obtained from the patient.

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Presentation

A 56-year-old woman presents with a two-year history of chronic persistent right upper quadrant abdominal pain that was associated with intermittent nausea, vomiting and unintentional weight loss. She has been on antihypertensive treatment, i.e. hydrochlorothiazide and amlodipine, for two years. Her blood pressure, 125/73mmHg, was well controlled and did not appear to be labile. She had tenderness in the right upper quadrant of the abdomen with no palpable masses. Oral analgesia was prescribed for the pain.

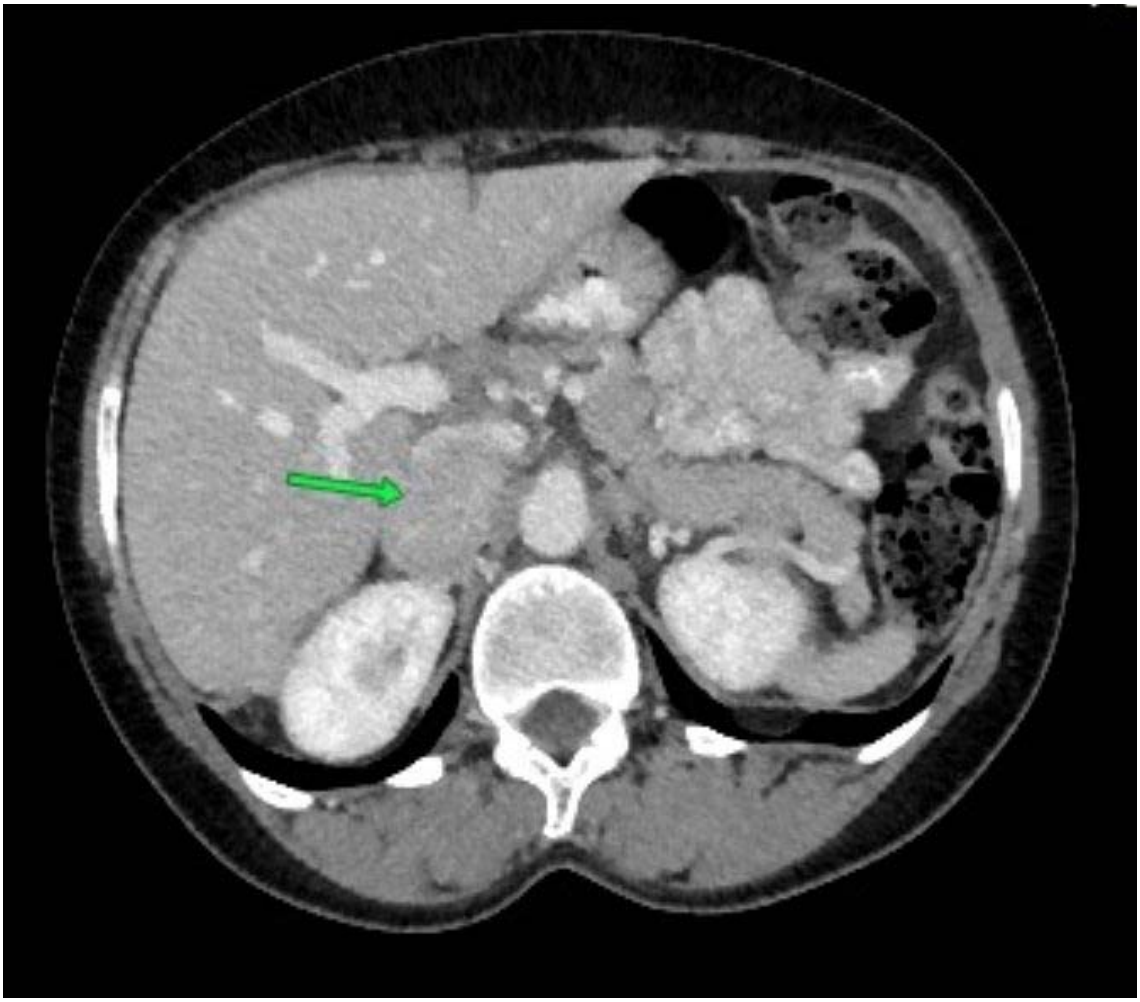

Figure 1. Axial post-contrast CT scan of the abdomen demonstrates a hyper enhancing mass of the right adrenal gland (arrow) displacing the inferior vena cava anteriorly.

Assessment

A computerised tomography (CT) scan demonstrated a 3.8 x 2.8 x 3.3cm hyperenhancing right retroperitoneal mass inseparable from the right adrenal gland (**Figure 1**). The mass was adjacent to the posterior inferior vena cava but did not appear to invade the vessel lumen. The findings were highly suspicious for a pheochromocytoma. There were no other significant findings on the CT scan.

Table 1: Comparison of the 24-hour urine fractionated metanephrines and normetanephrines

Biochemistry	**Normal range**	**0 Months**	**2 Months**	**8 Months**
Metanephrines (nmol/24hrs)	152-913	403	642	772
Normetanephrines (nmol/mmol)	699-2643	3887	1493	1246
Metanephrine : creatinine (nmol/mmol creatinine)	17-91	97	66	104
Normetanephrine : creatinine (nmol/mmol creatinine)	75-309	934	155	168

Diagnosis

The biochemical investigations confirmed a pheochromocytoma. The patient had elevated fractionated metanephrines and normetanephrines recorded on a 24-hour urine sample (**Table 1**). Urine vanillylmandelic acid (VMA) and the VMA : creatinine ratio were also raised at 234.3 µmol/24

hours (normal range 7-33µmol/24hours) and 56.3 µmol/24 hours (normal range 1.6-4.7 µmol/24hours), respectively. Multiple Endocrine Neoplasia type II was excluded.

Management

Two months later, while waiting for a right adrenalectomy, she presented unwell with persistent right upper quadrant abdominal pain which radiated to the epigastric region. She also presented with nausea, vomiting and melaena stools. She had been self-medicating with nonsteroidal anti-inflammatory medication. She had a labile blood pressure of 98/40mmHg and a heart rate of 69 beats/minute. She was anaemic with a haemoglobin of 6.4 g/dL (haemoglobin on initial presentation was 11.1 g/dL). She had severe right upper quadrant and epigastric tenderness. The patient received a gastroscopy which showed a large hiatus hernia with multiple gastric ulcers, Forrest classification III, with a normal duodenum. The patient was counselled appropriately and started on a proton pump inhibitor. She was transfused to a haemoglobin of 9.1g/dL and started on iron supplementation.

The anti-hypertensive medication was stopped (due to her low blood pressure), however her blood pressure remained hypotensive to normotensive, 94/50mmHg to 120/61mmHg. The hypotension with the severe abdominal pain was concerning for a possible haemorrhage or rupture of the adrenal tumour. A repeat contrasted CT of the abdomen demonstrated no change in size of the right adrenal mass but was now hypodense and minimally enhancing (**Figure 2**). There was no sign of haemorrhage within the mass. The features were suggestive of infarction with necrosis of the mass. The biochemical investigations were repeated with the fractionated metanephrines and normetanephrines within the normal reference ranges (refer to **Table 1**).

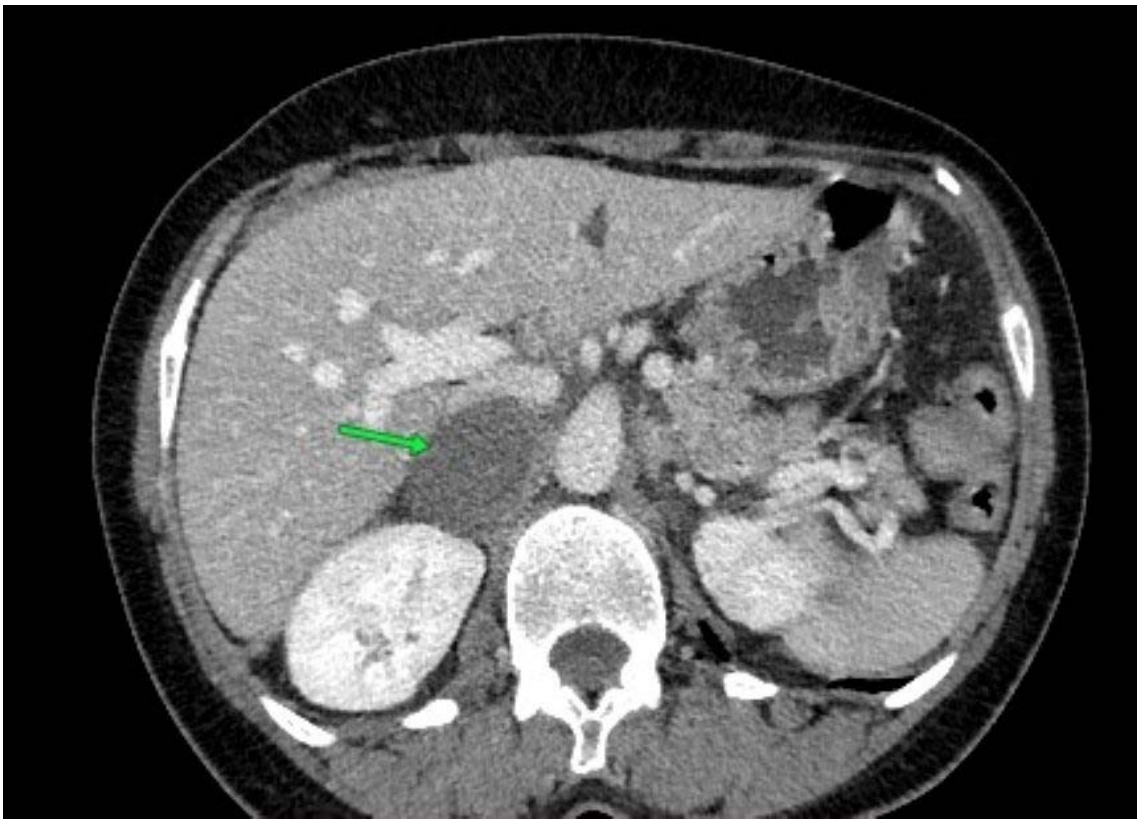

Figure 2. A second axial post-contrast CT scan of the abdomen, 2 months later, demonstrates a hypodensity with minimal enhancement (arrow) of the right adrenal mass.

The patient was followed-up again after 8 months and reported doing well. Her symptoms of abdominal pains, nausea and vomiting having resolved completely. Her biochemistry was repeated and found to be within the normal ranges (except for the metanephrine : creatinine ratio which was just above the reference range), with no features of a hypersecreting pheochromocytoma (refer to **Table 1**). The follow-up contrasted abdominal CT scan after 8 months showed minimal enhancement of a shrunken right adrenal mass (**Figure 3**). The mass now measures 12x18x17mm in keeping with involution post infarction.

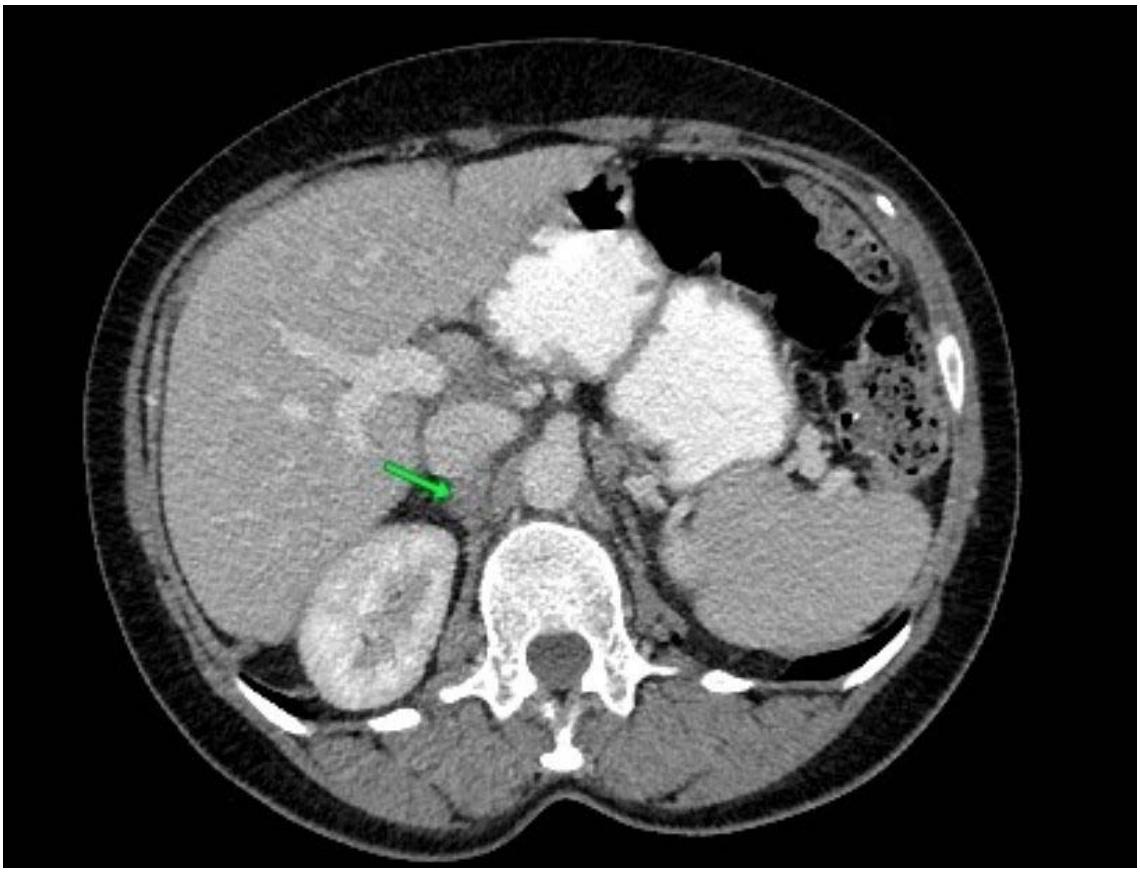

Figure 3. Axial post-contrast CT scan, 8 months after the second scan, shows minimal enhancement of the shrunken right adrenal mass.

Discussion

The typical symptoms of a pheochromocytoma includes the classic clinical triad of sweating, headaches and palpitations.[1] Atypical presentations have been reported up to 10% of pheochromocytomas, including hypocalcaemia, sexual dysfunction, haematemesis, erythrocytosis and acute abdomen.[2-6] Adrenal hemorrhage with/without rupture of the pheochromocytoma can present with hypotension or shock which is associated with a poor prognosis.[7]

Patients with pheochromocytoma have rarely been reported with clinical and biochemical features that resolve spontaneously.[8-10] These few reported cases all underwent an adrenalectomy, compared to our patient. The normalization of the biochemical values can be explained by changes

within the tumour where catecholamines can be endogenously metabolized.[11] This may occur in pheochromocytomas that are vascular and undergo cyst formation.[12] Normalization of the biochemical results can also be caused by extensive necrosis of the tumour, which may present with abdominal pain and contributing to our patient's symptoms.[12, 13] Coagulative necrosis due to ischemia has been explained as a result of catecholamine-induced vasoconstriction.[8] Spontaneous necrosis of pheochromocytomas have also been attributed to intravascular volume depletion,[3] desensitization of adrenergic receptors,[3] raised intracapsular pressure,[14] antihypertensive treatment resulting in hypotension[8] and hypocalcemia.[3] The cause for the spontaneous resolution in our patient was most likely due to tumour necrosis from hypotension and anaemia caused by the bleeding peptic ulcers. As the tumour infarcts, there can be further release of catecholamines causing further vasoconstriction and worsening of the infarction.[8]

The standard therapeutic management for pheochromocytomas is surgical resection.[15,16] However, the complication rate has been reported at 64.7% and mortality at 5.9%.[17] In our patient, the tumour was less than 4cm and did not have any radiological suspicion of malignancy. A comparison of international guidelines has demonstrated that an adrenal tumour with these parameters does not require surgical intervention, especially since the hyperfunctional status had resolved.[18] The patient was therefore managed conservatively. In view of this case, the question then arises if it would be possible and/or appropriate for a functional pheochromocytoma, that is less than 4cm with no suspicion of malignancy, to be managed with embolization instead of adrenalectomy.

Conclusion

Patients with pheochromocytomas may present with atypical symptoms. Spontaneous resolution of a pheochromocytoma is rare. Pheochromocytomas, that resolve spontaneously and are no longer hyperfunctional, can be managed non-operatively provided there is no risk of malignancy.

References

1. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. Endocrinology and Metabolism Clinics. 2011;40(2):295-311.

2. Rupala K, Mittal V, Gupta R, Yadav R. Atypical presentation of pheochromocytoma: Central nervous system pseudovasculitis. Indian J Urol. 2017;33(1):82-4.

3. Olson SW, Deal LE, Piesman M. Epinephrine-secreting pheochromocytoma presenting with cardiogenic shock and profound hypocalcemia. Annals of internal medicine. 2004;140(10):849-51.

4. Shi F, Sun L-X, Long S, Zhang Y. Pheochromocytoma as a cause of repeated acute myocardial infarctions, heart failure, and transient erythrocytosis: A case report and review of the literature. World Journal of Clinical Cases. 2021;9(4):951.

5. Ugur K, Girgin M, Bahcecioglu İH, Artas H, Selcuk Simsek F, Aydin S. An unusual case of hematemesis and epistaxis caused by a pheochromocytoma. Journal of International Medical Research. 2018;46(6):2470-3.

6. Chen H, Zhang Z, Zhang W, Yang F, Mao S, Wu Y, et al. Long-term sexual dysfunction and hypotensive shock in a patient with a pheochromocytoma. International Urology and Nephrology. 2022;54(6):1239-41.

7. Kobayashi T, Iwai A, Takahashi R, Ide Y, Nishizawa K, Mitsumori K. Spontaneous rupture of adrenal pheochromocytoma: review and analysis of prognostic factors. Journal of surgical oncology. 2005;90(1):31-5.

8. Ohara N, Uemura Y, Mezaki N, Kimura K, Kaneko M, Kuwano H, et al. Histopathological analysis of spontaneous large necrosis of adrenal pheochromocytoma manifested as acute attacks of alternating hypertension and hypotension: a case report. Journal of medical case reports. 2016;10:1-6.

9. Terai A, Terachi T, Yoshida S, Kadota K. Pheochromocytoma Presenting as Shock and Followed by Spontaneous Remission. Urologia Internationalis. 2010;44(1):58-60.

10. Suzuki T, Kawabe K, Mori C, Ueno A, Asakage H, Koiso K, et al. Pheochromocytoma with remission following phentolamine-induced shock. Urology. 1984;23(6):582-4.

11. Sarveswaran V, Kumar S, Kumar A, Vamseedharan M. A giant cystic pheochromocytoma mimicking liver abscess an unusual presentation–a case report. Clinical Case Reports. 2015;3(1):64.

12. Ng BW-L, Wong JS-L, Toh T-H. Biochemically normal adrenal pheochromocytoma following extensive central necrosis in a child with von Hippel-Lindau (VHL) gene mutation. BMJ Case Reports CP. 2021;14(12):e245154.

13. Mohamed HA, Aldakar MO, Habib N. Cardiogenic shock due to acute hemorrhagic necrosis of a pheochromocytoma: a case report and review of the literature. Can J Cardiol. 2003;19(5):573-6.

14. Nyman D, Wahlberg P. NECROTIC PHAEOCHROMOCYTOMA WITH GASTRIC HAEMORRHAGE, SHOCK, AND UNCOMMONLY HIGH CATECHOLAMINE EXCRETION. Acta Medica Scandinavica. 1970;187(1-6):381-3.

15. Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K. The North American Neuroendocrine Tumor Society Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Pheochromocytoma, Paraganglioma, and Medullary Thyroid Cancer. Pancreas. 2010;39(6):775-83.

16. Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JWM, et al. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. European Journal of Endocrinology. 2016;174(5):G1-G10.

17. Zorgani AE, Pirie FJ, Motala AA. Characteristics and outcome of patients with pheochromocytoma at a tertiary endocrinology clinic in Durban, South Africa over 14 years. Journal of Endocrinology, Metabolism and Diabetes in South Africa. 2018;23(2):52-8.

18. Jackson BS. Adrenal Incidentaloma Controversial Size Recommendations. Urol Res Pract. 2023;49(2):96-9.