SAGE Open Medical Case Reports
Volume 11: 1–4

DOI: 10.1177/2050313X231212095
journals.sagepub.com/home/sco
Sage

Left anterior descending artery disease in a 27-year-old with multiple endocrine neoplasia, type 2A: A case report

Mohammed Omar Al Salihi[1], Murali K Iyyani[1], Sarina Koilpillai[1], Gerson Quintero[1], Jorge Parellada[1] and SJ Carlan[2]

Abstract

Multiple endocrine neoplasia 2A is an autosomal dominant disease characterized by medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. Coronary artery disease is associated with the disorder, but the mechanism is unclear. A 27-year-old female presented with chest pain and palpitations. A left heart catheterization was performed and showed 80% stenosis of the left anterior descending artery. Imaging and workup also revealed primary hyperparathyroidism associated with a parathyroid adenoma and elevated serum and urine metanephrines and norepinephrines. A computed tomography of the abdomen revealed a large heterogeneous right adrenal mass measuring 7.9 cm × 6.8 cm × 8 cm consistent with a pheochromocytoma. The patient subsequently underwent adrenal mass resection and a complete thyroidectomy and parathyroidectomy. Early recognition and treatment of multiple endocrine neoplasia 2A can possibly reduce the risk of lethal heart disease in addition to the other associated endocrine disturbances.

Keywords

MEN 2A, pheochromocytoma, hyperparathyroid, coronary artery disease

Date received: 16 May 2023; accepted: 18 October 2023

Introduction

Multiple endocrine neoplasia 2A (MEN 2A) is an autosomal dominant disease characterized by medullary thyroid cancer (MTC), pheochromocytoma, and primary hyperparathyroidism. Most MEN 2A patients manifest germline mutations in the gene encoding the Rearranged during Transfection (RET) receptor tyrosine kinase,[1] with most mutations being missense mutations and, thereby, not coded.[2] The frequency of these endocrine tumors in MEN 2A is about 90% MTC, 10%–50% pheochromocytoma, and 10%–20% parathyroid hyperplasia.[3] The prevalence of MEN 2A mutation is about 1 in 35,000 individuals.[4] The primary cause of mortality in MEN 2A disease is the aggressiveness of the MTC.[5] Coronary artery disease (CAD) is primarily associated with pheochromocytoma and hyperparathyroidism in MEN 2A patients. Although the mechanism is still unknown, many theories have been proposed to explain the effect. Hypercalcemia has been associated with left ventricular hypertrophy (LVH), arrhythmias, vasoconstriction, and calcification of the myocardium, heart valves, and coronary arteries. Ogino showed that parathyroid hormone (PTH) has a vasodilatory effect and a direct positive chronotropic and indirect inotropic effects on the heart.[6] Schluter further suggested that PTH may act as a "hypertrophic factor" on myocardial muscle cells resulting in LVH.[7] The myocardial injury in pheochromocytoma may be mediated by excessive secretion of catecholamines which reduces blood flow via vasoconstriction. Other case studies have reported the presence of ST-segment elevation myocardial infarction in patients with pheochromocytoma crisis. Another possible explanation for CAD in pheochromocytoma is the hypercoagulability induced by pheochromocytoma leading to thrombosis in the coronary arteries.[8] Here we report an unusual

[1]Department of Internal Medicine, Orlando Health, Orlando, Florida, USA
[2]Division of Academic Affairs and Research, Orlando Health, Orlando, Florida, USA

Corresponding Author:
SJ Carlan, Division of Academic Affairs and Research, Orlando Health, 1401 Lucerne Terrace, 2nd Floor, Orlando, FL 32806, USA.
Email: stevecarlan@gmail.com

Table 1. Laboratory findings with normal value range for comparison.

Lab test	Lab value
Troponin	0.98 ng/mL (0.00–0.05 ng/mL)
TSH	0.40 uiU/mL (0.45–5.33 uIU/mL)
Free T4	1.07 ng/dL (0.61–1.12 ng/dL)
Calcium	11.1 (8.6–10.3 mg/dL)
Magnesium	<0.5 mg/dL (1.9–2.7 mg/dL)
PTH	371 pg/mL (12–88 pg/mL)
Calcitonin	779 pg/mL (⩽7.6 pg/mL)
Serum metanephrines	33 nmol/L (<0.50 nmol/L)
Serum normetanephrines	176 nmol/L (<0.90 nmol/L)
Urine metanephrines	16,688 μg/g Cr (29–158 μg/g Cr)
Urine normetanephrines	40,875 μg/g Cr (81–330 μg/g Cr)

Mcg: micrograms; nmol: nanomoles; L: liter; mg: milligrams; dL: deciliter; uiU: micro international units, TSH: thyroid stimulating hormone; PTH: parathyroid hormone.

case of typical MEN 2A disease in a 27-year-old female diagnosed with a left anterior descending (LAD) artery disease requiring invasive treatment.

Case

A 27-year-old female with a past medical history of hypertension and hyperthyroidism presented with bilateral lower extremity weakness, chest pain, and palpitations for 1 day. She described the pain as left-sided, non-radiating, and non-exertional. The patient reported previous episodes of elevated heart rate for which she was evaluated at outside medical centers, however she did not recall the diagnosis. Based on previous medication, she was noncompliant for 2 months on metoprolol. Her family history was negative. The patient was not on any medications like amiodarone-causing hyperthyroidism, physical examination was benign with no signs of thyroiditis, and the patient denies any exogenous uptake of Iodine or thyroid hormone. Her initial vital signs revealed hypertension with a blood pressure of 165/95 mmHg and tachycardia with a heart rate of 130 beats per min (bpm). On physical examination, heart rate was tachycardic but with regular rhythm. The chest wall was nontender to palpation. Her BMI (body mass index) was 15.8 and the remainder of the physical examination was benign.

The initial laboratory tests were significant for elevated troponin, low thyroid stimulating hormone (TSH), normal free thyroxine (T4), hypercalcemia, and hypomagnesemia (Table 1). Electrocardiogram (EKG) revealed sinus tachycardia with a ventricular rate of 113 beats per min. The patient was diagnosed with a non-ST elevation myocardial infarction and a cardiologist was consulted. A left heart catheterization (Figure 1) revealed an 80% stenosis of the LAD artery. A drug-eluting stent (DES) was placed, and the patient was started on dual antiplatelet therapy with aspirin, clopidogrel, and high-intensity statin therapy.

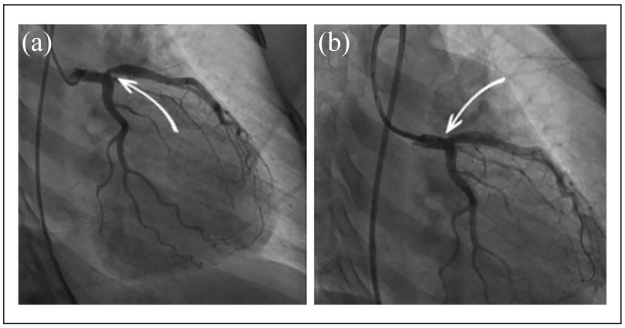

Figure 1. (a) Severe 80% stenosis of the ostial LAD artery. (b) Successful PTCA and DES placed in the ostial LAD artery, post dilation with balloon reducing 80% to 0% stenosis.
LDA: Left anterior descending; PTCA: percutaneous transluminal coronary angioplasty; DES: drug-eluting stent.

A thyroid ultrasound was then performed to evaluate decreased TSH levels further, which showed bilateral thyroid nodules measuring up to 1.7 cm. Further workup for hypercalcemia revealed significantly elevated PTH and normal vitamin D levels, denoting a diagnosis of primary hyperparathyroidism (Table 1). The hypercalcemia and hypomagnesemia were the only complications of her primary hyperparathyroidism. A nuclear medicine parathyroid scan was ordered, which revealed a 1.6 cm soft tissue density in the left cervical neck, consistent with attributes of a parathyroid adenoma.

Additionally, given the presence of hypertension in a young patient, a workup was initiated for secondary causes of hypertension. Serum and urine metanephrines and norepinephrines were very elevated (Table 1). Computed tomography of the abdomen was evaluated for pheochromocytoma and revealed a large heterogeneous right adrenal mass measuring 7.9 cm × 6.8 cm × 8 cm. Given the presence of thyroid nodules, primary hyperparathyroidism, and likely pheochromocytoma, there was concern for possible MEN 2A syndrome. Serum calcitonin levels were analyzed and were found to be significantly elevated at 779 pg/mL (picograms per milliliter (⩽7.6 pg/mL)), which raised concerns for MTC. Given the triad of primary hyperparathyroidism, MTC, and suspected pheochromocytoma, the patient was presumptively diagnosed with MEN 2A syndrome. An oncologist was consulted, and outpatient follow-up was recommended after surgical evaluation. General surgery was considered for pheochromocytoma removal, and the patient was started on doxazosin for 3 weeks for an effective alpha blockade. The patient subsequently underwent adrenal mass resection by laparotomy, whose pathology revealed a benign pheochromocytoma. Head and neck surgery was then consulted for surgical evaluation of MTC and parathyroid adenoma. The patient underwent a total thyroidectomy, parathyroidectomy, left neck dissection, and bilateral central neck dissection 16 days after pheochromocytoma removal. All the nodes were negative for malignancy except the left

neck Level IV, dissection. One of seven lymph nodes with metastatic MTC, 4.0 millimeters in greatest dimension. Extracapsular extension was not identified. The intraoperative PTH level after surgical resection of the parathyroid adenoma was 11 pg/mL (milliliter). Thyroid pathology was consistent with MTC. The patient tolerated both procedures well and demonstrated steady improvement in hypertension, tachycardia, and calcium levels. After parathyroidectomy, PTH went as low as 1 pg/ml and the Ionized calcium went to 0.99 mmol/ml, and patient required calcitriol. The patient was started on levothyroxine, calcitriol, and oral calcium and discharged with genetic counseling follow-up.

Discussion

This patient was diagnosed with CAD and pheochromocytoma while hospitalized. The uniqueness of this case lies in the manifestation of three diseases constituting MEN 2A in a young female, all of which were diagnosed within a year and associated with a target organ disease of her endocrinopathy, that is, heart. The chief complaint for visiting the hospital was bilateral lower extremity weakness. Her troponin level was elevated; therefore, cardiac catheterization was ordered, revealing the blockage. Our case suggests a probable correlation between MEN 2A and CAD. Previous studies have demonstrated a direct effect of the MEN 2A disease on the heart, most specifically coronary arteries. Koubaity have demonstrated hyperparathyroidism's association with increased coronary calcium scores.[9] However, pheochromocytoma is more associated with CAD, with the first case reported in 1952 of a 22-year-old farmer afflicted with a fatal myocardial infarction who died on the 5th day of hospital admission.[10] Bourke considered that myocardial toxicity in pheochromocytoma patients is secondary to increased demand caused by the intense adrenergic stimulation leading to myocardial damage with infarction and polymorphic cell infiltration.[11] The heart and the coronaries can be damaged by the MEN 2A syndrome in multiple ways. MTCs can metastasize to the myocardium, especially in aggressive cancers.[12] Hyperparathyroidism can cause heart disease in multiple ways, as well. First, it can change the endothelium's vasodilatory properties, leading to hypertension.[13] Second, the parathyroid hormone can cause upregulation of the protein kinase C pathway leading to ventricular hypertrophy, especially in the left ventricle.[14] Third, those patients can develop the risk of heart failure due to cardiac myocyte hypertrophy and endothelial and vascular dysfunction.[15] Fourth, calcium can deposit in the coronary artery media and intima, leading to calcific disease. Pheochromocytoma can also cause CAD, although the underlying mechanism may be complex. Three theories have been proposed for the mechanism. The first theory explores excess catecholamine that leads to increased levels of factor 8 and von Willebrand factor and causes platelet activation. According to the second theory, CAD can also be caused by increased plasminogen activator inhibitor-1, co-released with catecholamine. The third theory considers the vasospasm that causes microvascular dysfunction secondary to increased catecholamine secretion.

Conclusion

Diagnosing MEN 2A can be challenging. In patients with ACS (acute coronary syndrome) and one component of MEN 2A syndrome, a complete workup should be performed to rule out other MEN 2A tumors as early diagnosis is the key to management and follow-up. A multidisciplinary approach with close communication between endocrinologist, primary care physician, and the cardiologist is important to achieve optimized outcomes for such patients.

Acknowledgements

None.

Author contributions

M.O.A.S. contributed to the study design, data collection, article preparation, and literature search. M.K.I. contributed to the interpretation of data and article preparation. S.K., S.J.C., and G.Q. contributed to article preparation and literature search. J.P. was involved in data collection and literature search.

Data availability statement

All authors had access to the data and a role in writing the article, no disclaimers.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt. IRB was not notified as it is a case report and the data have been anonymized.

Informed consent

Written informed consent to publish was obtained.

ORCID iD

SJ Carlan https://orcid.org/0000-0001-9867-8538

References

1. Wells SA, Pacini F, Robinson BG, et al. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. *J Clin Endocrinol Metab* 2013; 98: 3149–3164.

2. Mulligan L, Kwok J, Healey C, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. *Nature* 1993; 363: 458–460.
3. Wells SA Jr, Asa SL, Dralle H, et al. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015; 25: 567–610.
4. Young WF. Secondary Hypertension: Pheochromocytoma and Paraganglioma. In: Bakris GL and Sorrentino M (eds). *Hypertension: A companion to Braunwald's heart disease*. Amsterdam: Elsevier Inc., 2007, pp. 119–133.
5. Grey J and Winter K. Patient quality of life and prognosis in multiple endocrine neoplasia type 2. *Endocr Relat Cancer* 2018; 25: T69–T77.
6. Ogino K, Burkhoff D and Bilezikian JP. The hemodynamic basis for the cardiac effects of parathyroid hormone (PTH) and PTH-related protein. *Endocrinology* 1995; 136: 3024–3030.
7. Schluter KD and Piper HM. Trophic effects of catecholamines and parathyroid hormone on adult ventricular cardiomyocytes. *Am J Physiol-Heart Circ Physiol* 1992; 263: H1739–H1746.
8. Chen F, Zheng M, Li X, et al. ST-segment elevation myocardial infarction related to potential spontaneous coronary thrombosis in pheochromocytoma crisis. *Front Endocrinol* 2020; 11: 140.
9. Koubaity O, Mandry D, Nguyen-Thi PL, et al. Coronary artery disease is more severe in patients with primary hyperparathyroidism. *Surgery* 2020; 167: 149–154.
10. Priest WM. Phaeochromocytoma with fatal myocardial infarction in a man aged 22. *Br Med J* 1952; 2(4789): 860–862.
11. Bourke SJ, Wilkes G, Maloney DL, et al. Phaeochromocytoma-induced myocardial necrosis. *Scott Med J* 1991; 36: 184.
12. El Ghannudi S, Germain P, Schneegans O, et al. Cardiac metastasis from medullary thyroid carcinoma: insights from multimodal molecular imaging and magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2020; 21: 231–232.
13. Yao L, Folsom AR, Pankow JS, et al. Parathyroid hormone and the risk of incident hypertension: the atherosclerosis risk in communities study. *J Hypertens* 2016; 34: 196–203.
14. Schlüter KD, Weber M and Piper HM. Parathyroid hormone induces protein kinase C but not adenylate cyclase in adult cardiomyocytes and regulates cyclic AMP levels via protein kinase C-dependent phosphodiesterase activity. *Biochem J* 1995; 310: 439–444.
15. Bansal N, Zelnick L, Robinson-Cohen C, et al. Serum parathyroid hormone and 25-hydroxyvitamin D concentrations and risk of incident heart failure: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc* 2014; 3(6): e001278.