Multiple endocrine neoplasia 2A syndrome presenting as peripartum cardiomyopathy due to catecholamine excess

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Abstract
We report the case of a 24-year-old female with a history of medullary thyroid carcinoma who presented at 38 weeks gestation with acute chest pain and shortness of breath. She was found to be in pulmonary edema and respiratory failure. An emergency cesarean section was performed. Subsequently, an echocardiogram revealed an ejection fraction of 10%. After medical therapy with digoxin, milrinone, captopril and diuretics, her condition improved rapidly and a repeat echocardiogram showed that the left ventricular function had normalized. Diagnosis of pheochromocytoma was made by urine and plasma catecholamine measurements. Magnetic resonance imaging revealed a 3.7 cm left adrenal mass. Increased uptake activity was seen in the same region by an ¹³¹I-metaiodobenzylguanidine (MIBG) scan. The patient underwent successful surgical resection of the pheochromocytoma. Subsequent DNA analysis revealed that the patient had a mutation of the RET proto-oncogene. The same mutation was also found in several of her family members.

In summary, we report a case of multiple endocrine neoplasia 2A presenting as peripartum cardiomyopathy and cardiovascular collapse. Pheochromocytoma should be considered as a potential cause of peripartum cardiomyopathy.

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Introduction
Pheochromocytoma presenting as cardiogenic shock is a recognized but relatively uncommon occurrence, with only a few published cases (1, 2). We report an unusual case of a 24-year-old pregnant woman with a history of medullary thyroid carcinoma who presented with peripartum cardiomyopathy as a result of catecholamine release from a pheochromocytoma. She had a rapid resolution of her cardiac dysfunction after only 5 days of medical therapy. Further investigations confirmed the diagnosis of multiple endocrine neoplasia 2A (MEN-2A).

Patient report
The patient was a 24-year-old Hispanic female (gravid2, para1), who presented at 38 weeks gestation to another hospital with complaints of acute chest pain and shortness of breath. In addition, she had neck pain, and nausea with vomiting. Her pregnancy had thus far been complicated only by cholestasis during her third trimester, for which she was taking cholestyramine.

It was found that the patient had had medullary thyroid carcinoma at age 21 for which she had had a thyroidectomy. Her obstetrical history was significant for a missed abortion one year earlier. Medication consisted of l-thyroxine (L-T4; 150 μg/day) and cholestyramine. She had no allergies and denied tobacco, alcohol, and illicit drug use. Significant family history revealed a mother who died during childbirth.

The patient was brought in to the labor and delivery suite; however, she was found not to be in labor. She was afebrile with a pulse of 84 beats/min, a blood pressure of 124/84 mmHg, and a respiratory rate of 28 breaths/min. Wheezes and rales were present throughout both lung fields, with poor air movement. Initial arterial blood gas measurement, while on 6 liters of oxygen by nasal cannula, showed pH of 7.43, PaCO₂ of 29 mmHg, PaO₂ of 105 mmHg, and oxygen saturation of 96%. An electrocardiogram revealed sinus tachycardia with diffuse ST depression anterolaterally in leads V₂ through V₆. Despite being given nebulized albuterol treatments, her respiratory distress worsened and she was intubated. A chest x-ray revealed bilateral pulmonary edema. Fetal bradycardia prompted an emergency cesarean section. A liveborn female weighing 3660 g was delivered, with Apgar scores of 4 at 0 min, 6 at 1 min, and 6 at 5 min. The patient was then taken to the intensive care unit.

Her initial blood analysis at the outside institution was remarkable for a glucose of 18.4 mmol/l (normal 4.2–6.4) and a calcium of 1.7 mmol/l (normal
Urinalysis showed 300 mg/l protein and >10 g/l glucose. Total creatine kinase was slightly elevated at 350 IU/l (normal 22–269), with a creatine kinase MB isoenzyme fraction of 10.8 μg/l (normal 0–4) and a troponin I level of 0.97 μg/l (normal 0–0.5). The thyrotropin level was elevated at 31.4 mU/l (normal 0.35–5.5). Hepatic function panel was remarkable for a serum glutamic oxaloacetic transaminase (SGOT) level of 79 IU/l (normal 0–40), serum glutamic pyruvic transaminase (SGPT) of 128 IU/l (normal 0–50), and alkaline phosphatase of 227 IU/l (normal 25–115).

After the cesarean section, the patient became hypotensive and tachycardic. An echocardiogram revealed poor left ventricular function with an ejection fraction of approximately 10%. Coronary angiography showed no abnormalities. An intra-aortic balloon pump (IABP) and a Swan Ganz catheter were placed, but she continued to be tachycardic at 140 beats/min and hypotensive with systolic blood pressures of 70–80 mmHg, not augmenting with the IABP. Pulmonary capillary wedge pressure was 13 mmHg, cardiac output was 1152 dynes/s/cm², and systemic vascular resistance was 5.1 ml/min/m². The patient was intubated and sedated, but arousable. Her neck examination revealed no jugular venous distension, and a well-healed thyroidectomy scar with no palpable thyroid tissue or other masses. Diffuse rhonchous breath sounds were present bilaterally. Abdominal examination showed a clean, dry cesarean section wound. A repeat echocardiogram again revealed a moderately dilated left ventricle with severe global systolic dysfunction with an ejection of 10%. Captopril was started, milrinone was continued, and l-T₄ was given intravenously.

Given the history of medullary thyroid carcinoma, the possibility of pheochromocytoma and MEN-2A was considered. The patient and her family were further questioned, and it was discovered that the patient’s mother had died during childbirth under circumstances that were very similar to the current situation. The patient did acknowledge having rare episodes of intermittent diaphoresis, palpitations and weakness lasting a few minutes over the last few years. Therefore, urine was collected for immediate analysis.

Upon arrival at our institution, the patient was afebrile, with a heart rate of 120 beats/min, and blood pressure of 80/50 mmHg. Pulmonary capillary wedge pressure was 13 mmHg, cardiac output was 1152 dynes/s/cm², and systemic vascular resistance was 5.1 ml/min/m². The patient was intubated and sedated, but arousable. Her neck examination revealed no jugular venous distension, and a well-healed thyroidectomy scar with no palpable thyroid tissue or other masses. Diffuse rhonchous breath sounds were present bilaterally. Abdominal examination showed a clean, dry cesarean section wound. A repeat echocardiogram again revealed a moderately dilated left ventricle with severe global systolic dysfunction with an ejection of 10%. Captopril was started, milrinone was continued, and l-T₄ was given intravenously.

Figure 1 T2-weighted MRI reveals a 3.7 cm high signal intensity mass in the left adrenal gland, with a central cystic area, characteristic of a pheochromocytoma.
catecholamine determination, and a 24 h urine collection was begun. The spot urine showed elevated norepinephrine of 93.4 µg/g creatinine (normal level 7–65) and epinephrine of 58.2 µg/g creatinine (normal 2–16), and a normal dopamine of 92.3 µg/g creatinine (normal 40–390). While awaiting the results of the 24 h urine collection, an abdominal ultrasound was carried out that revealed a left suprarenal mass posterior to the splenic vein, measuring 3.2 × 4.6 cm.

Blood pressure remained stable and milrinone was discontinued on hospital day 2. The patient was extubated on the third day. A repeat transthoracic echocardiogram carried out on the fifth hospital day revealed normal left ventricular systolic function and wall motion. Given the remarkable resolution of her cardiac function, peripartum cardiomyopathy was deemed unlikely, and the suspicion for a pheochromocytoma increased. An abdominal magnetic resonance imaging (MRI) scan revealed a left-sided, 3.7 cm adrenal mass with low signal intensity on T1- and high signal intensity on T2-weighted images, consistent with a pheochromocytoma (see Fig. 1). The patient’s urine and plasma laboratory values confirmed the diagnosis of pheochromocytoma (Table 1). Additionally, her parathyroid hormone (PTH) level was found to be 9 ng/l (normal <60) with a simultaneous calcium level of 1.85 mmol/l (normal 2.2–2.6). Her plasma metanephrine level was 2.89 nmol/l (normal 0–0.49) and plasma normetanephrine level was 2.9 nmol/l (normal 0–0.89). Calcitonin level was <0.03 ng/l.

A computerized tomography (CT) scan again revealed the left adrenal mass, and there was no evidence of extra-adrenal involvement. An 131I-metaiodobenzylguanidine (MIBG) scan revealed markedly increased activity in the left suprarenal region and a mild focus of activity in the right suprarenal region (Fig. 2). While the activity in the left adrenal area corresponded with the mass, there was no mass seen on MRI or CT scans in her right suprarenal region. Captopril was discontinued and α-blockade with phenoxybenzamine was initiated. The genetic counseling service was consulted and the patient’s DNA was collected and sent to test for mutations known to correspond with the mass, there was no mass seen (Fig. 2).

Table 1 Twenty-four hour urine catecholaminess and metanephrines on hospital days 1, 5 and 8. Abnormal values are shown in bold type.

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 8</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>103</td>
<td>54</td>
<td>30</td>
<td>15–80 µg/day</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>72</td>
<td>40</td>
<td>21</td>
<td>0–20 µg/day</td>
</tr>
<tr>
<td>Dopamine</td>
<td>69</td>
<td>92</td>
<td>95</td>
<td>65–400 µg/day</td>
</tr>
<tr>
<td>Normetanephrine</td>
<td>2002</td>
<td>967</td>
<td>773</td>
<td>&lt;900 µg/day</td>
</tr>
<tr>
<td>Metanephrine</td>
<td>3978</td>
<td>1775</td>
<td>1696</td>
<td>&lt;400 µg/day</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>5980</td>
<td>2742</td>
<td>2469</td>
<td>&lt;1300 µg/day</td>
</tr>
</tbody>
</table>

Ten days later, she returned for a left adrenalectomy. During the operation, the right adrenal gland was palpated and felt to be normal. During manipulation of the left adrenal mass, the patient became slightly hypertensive with 160 mmHg systolic pressure and was given nitroglycerin. Upon clamping of the mass, the patient had an immediate hypotensive response with a systolic pressure of 80 mmHg, requiring an epinephrine drip. Postoperatively, the patient did well. The patient was weaned off the epinephrine drip on the same day. She was discharged on postoperative day 4. Pathology revealed a benign pheochromocytoma, weighing 27 g and measuring 6.5 × 5.0 × 1.5 cm (Fig. 3). Results of repeat urine catecholamine measurements 1 month later were normal.

Commercial polymerase chain reaction (PCR)-based assay and DNA sequence analysis were used to search for the presence of a mutation in exons 10, 11, 13, 14 and 16 of the RET proto-oncogene. A mutation was identified in codon 634 (TGC → TAC) with predicted amino acid change Cys → Tyr. The presence of this mutation was consistent with the diagnosis of MEN-2A. Additional genetic screening was performed on her brothers and sisters (Fig. 4). Four of her six siblings were found to have the same mutation.

**Discussion**

Several cases of catecholamine-induced cardiomyopathy as well as pheochromocytoma in pregnancy have been described. However, pheochromocytoma-induced cardiomyopathy in the peripartum period, as seen in our patient, has only been described in fewer than ten cases (2, 3–7). Furthermore, our patient’s pheochromocytoma was part of the MEN-2A syndrome, with implications for her and her first-degree relatives, as we will review below.

Catecholamines can cause both dilated or hypertrophic cardiomyopathy (8–11); however the specific mechanism is not known. It has been suggested that elevated catecholamines and/or their oxidation products cause increased permeability of the sarcolemmic membrane, which causes an influx of calcium that results in myocardial necrosis (12–14). Others suggest that excess adrenergic stimulation causes vasoconstriction that leads to decreased coronary perfusion resulting in myocarditis (11, 12, 14, 15). It is likely that both
mechanisms contribute to myocardial injury. Histologically, focal myofiber necrosis, myofibrillar degeneration, myocardial fibrosis, and mononuclear infiltration have been observed (1, 3, 6, 7, 10, 13). Pulmonary edema seen in pheochromocytoma may be cardiogenic, but there may also be a noncardiogenic component. Catecholamines are thought to cause pulmonary capillary membrane damage leading to increased microvascular permeability, coupled with postcapillary venule constriction. This leads to increased pulmonary capillary hydrostatic pressure and pulmonary edema (15).

Pheochromocytoma-induced postpartum cardiomyopathy has been reported by two groups (3, 5). Another report described a case that presented with severe hypertension, cardiomyopathy, and pulmonary edema during the first trimester (4). Our patient, however, did not present with a hypertensive crisis but rather a low/normal blood pressure, possibly due to the predominantly epinephrine secreting nature of her tumor. It has been hypothesized that uterine contraction, as well as increased intra-abdominal pressure and even vigorous fetal movement, may play a role in initiating symptoms of pheochromocytoma in pregnancy (3, 16), and perhaps these instigated our patient’s acute event.

Pheochromocytoma during pregnancy is potentially very dangerous to both mother and fetus, due to the effects of catecholamines on blood pressure and uteroplacental blood flow (16, 17). Antenatal recognition reduces maternal mortality from 17% to 0% and fetal mortality from 50% to 15% (17). However, given the similarity of many of the symptoms to pre-eclampsia, such as hypertension, headache, postural hypotension, and heart failure, many cases remain undiagnosed. In addition, the occurrence of hypertension and classical symptoms of catecholamine excess are less frequent.

Figure 2 Chest and abdominal images were acquired 48 h after the administration of 2.11 mCi 131I-MIBG. The image demonstrates markedly increased activity in the left suprarenal region corresponding to the site of the 3.7 cm adrenal mass identified on MRI. There is also a mild focus of activity in the right suprarenal region.

Figure 3 Left adrenal containing the pheochromocytoma. (A) Gross appearance of 26.7 g of tissue containing a nodule with a peripheral rim of normal adrenal tissue. (B) Microscopic appearance of the pheochromocytoma with typical uniform cells containing abundant cytoplasm and small, central nuclei. Note that the cells are separated into clusters by fibrovascular stroma.
than in non-pregnant women (16). These cases may also be discovered when there are unusual responses to drugs that affect catecholamines, or as reactions to anesthesia, labor, or delivery. The possibility of pheochromocytoma should be entertained in any pregnant woman with intermittent hypertension occurring during the first half of pregnancy or accompanied by headache, palpitations, tachycardia, diaphoresis, and impaired glucose tolerance or diabetes. In addition, suggestive family history for pheochromocytoma or familial syndromes associated with the tumor or sudden collapse should also raise suspicions (16).

Another unusual aspect of this case is the rapidity of the reversal of the cardiomyopathy. In most reported cases, post-resection resolution of cardiomyopathy takes several months to occur (1, 2, 10, 18-20). However, medical therapy with an α-blocker, angiotensin converting enzyme (ACE) inhibitor, and/or β-blocker has been reported to reverse the condition in 3-14 days (3, 6, 11, 13, 21). Our patient’s left ventricular function improved from 10% to 60% in 5 days. The improvement could not be attributed to α-blockade, which was started after resolution of the cardiomyopathy had already been demonstrated. Rather, it was likely due to the administration of captopril alone, as described previously (22).

Our patient’s pheochromocytoma is familial, as part of the MEN-2A syndrome, an autosomal dominant condition that includes medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. Medullary thyroid cancer is usually the first manifestation of MEN-2A due to its earlier occurrence and higher penetrance (23). Before MEN-2A was recognized as a syndrome, one of the most frequent causes of death in patients with medullary thyroid cancer was sudden death from pheochromocytoma (24, 25). With the recognition of MEN-2A as a syndrome, screening for pheochromocytoma has become more widespread, resulting in earlier detection, improved management, and lower mortality (23). This has led to the recommendation that anyone diagnosed with medullary thyroid cancer be screened for the RET proto-oncogene and for pheochromocytoma (23), even before surgery for medullary thyroid cancer is performed (24).

There are several unique features of pheochromocytoma that occur in MEN-2A compared with sporadic cases. Early symptoms in familial pheochromocytoma include intermittent palpitations, tachycardia, and nervousness, rather than diaphoresis or headache (26). Also, hypertension is less common in pheochromocytoma associated with MEN-2, occurring in only a third of patients (27) compared with the usual 72% (28). In addition, the tumor has an increased production of epinephrine, with an increased urinary epinephrine as well as an increased ratio of epinephrine to norepinephrine (29). Finally, in MEN-2 patients who have a unilateral pheochromocytoma, the unaffected adrenal gland has a 50% chance of developing pheochromocytoma in 10 years (16, 30).

Mutations of the RET proto-oncogene, found in MEN-2 syndromes, are gain-of-function mutations, causing activation of the receptor, tyrosine kinase. This results in hyperplasia of calcitonin-producing parafollicular cells and adrenomedullary chromaffin cells, and a subsequent neoplastic transformation (31). The specific RET mutation correlates with the MEN-2 variant and the aggressiveness of the medullary thyroid cancer (23), and can thus be used to stratify risk and guide tumor screening in carriers. A mutation in codon 634 places this family in level two, which is described as ‘high risk’ for medullary thyroid cancer. It is recommended that the affected individuals have a total thyroidectomy before the age of five, yearly screening for pheochromocytoma starting at age five, and annual monitoring of calcium and PTH levels. Pheochromocytomas occur more frequently in codon 634
mutation carriers (up to 50%) and also occur at an earlier age and are more likely to be bilateral (in about 25%) (23, 32). All female MEN-2 carriers should be screened for a pheochromocytoma prior to or early during pregnancy (23), as antenatal diagnosis decreases both fetal and maternal mortality.

Our patient had surgery for medullary thyroid cancer when she was 21 years old. It is not clear whether or not she was screened for the RET proto-oncogene mutation or for pheochromocytoma at that time. Such testing would have been appropriate. Furthermore, if the RET proto-oncogene mutation had been discovered upon the diagnosis of the medullary thyroid cancer, screening for pheochromocytoma should have been performed yearly thereafter, and especially upon the discovery of her pregnancy (23).

Increased MIBG activity seen in bilateral adrenal glands of this patient raised the possibility of bilateral pheochromocytoma. However, the increased uptake may be seen in any situation of adrenal medullary hyperfunction, including adrenal medullary hyperplasia. Microscopic adrenal hyperplasia occurs in MEN-2A and -2B patients, both adjacent to the pheochromocytoma and also in the contralateral adrenal gland, although it may never develop into a tumor (30, 33). Some advocate prophylactic bilateral adrenalectomy in patients with unilateral pheochromocytomas that occur as part of the MEN-2 syndrome. However, it has been found that unilateral adrenalectomy and close monitoring of symptoms and biochemical changes may be safer given that bilateral adrenalectomy poses the risk of a permanent Addisonian state (30). Because our patient's right adrenal appeared normal on intra-operative examination, it was decided that total adrenalectomy would not be performed and she would be closely monitored.

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References


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