

Case of Chronic Indolent Pheochromocytoma That Caused Medically Controlled Hypertension but Treatment-Resistant Diabetes Mellitus

HyunJung Lee, Anna F. Dominiczak, Garry L.R. Jennings, Eun Joo Cho, Hae-Young Lee

A 47-year-old woman visited the emergency room in March 2006. Her main complaint was dyspnea, which began 2 months before. She was a previously healthy woman, but after upper respiratory infection 2 months before, she developed symptoms of cough, myalgia, epigastric pain, and dyspnea of New York Heart Association functional class II to III with intermittent chilling. She was managed at the local clinic for asthma, but there was no improvement in symptoms.

One month before the emergency room visit, she had a procedure for anal hemorrhoids and bled severely and received transfusion. Three days before visiting the emergency room, cough and dyspnea deteriorated. She went to the local hospital, was diagnosed with heart failure, and was referred to the emergency room. There was nothing notable in her medical history. She was a housewife, nonsmoker, and did not drink alcohol. She had nothing of interest in her family history.

On interview, she had general weakness and easy fatigability. She also had anorexia, indigestion, and some weight loss. She continued to have cough and dyspnea, which aggravated on supine position and on exertion. On physical examination, she had normal blood pressure (BP) at 129/86 mm Hg. Heart rate was slightly elevated at 113 bpm, and her breathing was rather fast at 22 times per minute. Body temperature and oxygen saturation were normal. Her height was 161 cm, and her weight was 67 kg; she was overweight.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The patient was slightly anemic and icteric on examination. She was not dehydrated. On auscultation, coarse breath sounds with crackles in the right lower lung field, and rapid heartbeat with a soft systolic murmur could be heard. Abdomen was soft and flat without any tenderness, and no visible edema or cyanosis. Arterial blood gas analysis done at room air indicated normal O₂ pressure and signs of hyperventilation. She had slight leukocytosis with a normal segmented fraction.

Total bilirubin was elevated at 2.6 mg/dL. Liver enzymes were elevated at aspartate transaminase 930 U/L and alanine transaminase 1868 U per liter. Prothrombin time international normalized ratio (PT INR) was elevated at 1.59, and her urine was rather concentrated, and proteinuria was 2+ on dipstick. B-natriuretic peptide level was 2002 pg/mL. Glycosylated hemoglobin (HbA1c) level was 6.8%, and fasting blood sugar was 142 mg/dL, and later, she was newly diagnosed with diabetes mellitus. Thyroid function was normal, and hepatic serology was normal.

Initial chest x-ray showed cardiomegaly and pulmonary congestion with right pleural effusion (Figure 1A). The initial ECG showed sinus tachycardia with ST elevation at V₁ through V₃ and ST depression at V₆, suggesting a left ventricular hypertrophy (Figure 2). Her initial echocardiogram was as follows: she had dilated left ventricular cavity with an end-systolic dimension of 61 mm and an end-diastolic dimension of 72 mm, and wall thickness was normal. There was global hypokinesia with secondary mitral regurgitation because of tethering, and ejection fraction was decreased at 28% (Movies S1 through S4 in the [online-only Data Supplement](#)).

A myocardial single positron emission computed tomography was performed to check for cause of heart failure (Figure 3). There was no significant perfusion decrease suggesting ischemic heart disease.

Differential Diagnosis

ECG showed ST elevation and less focal change, but there was global hypokinesia and no specific regional wall motion abnormality. We ruled out coronary artery disease by SPECT.

Thus, the initial assessment was dilated cardiomyopathy aggravated by a cold with congestive hepatomegaly and newly diagnosed diabetes mellitus.

She was admitted to the ward on dobutamine support and parenteral diuretics. Her symptoms improved after hemodynamic stabilization, weight reduction of 4 kg with diuretics, and addition of angiotensin-converting enzyme inhibitor and β -blocker. She was discharged after 1 week; at time of discharge, her BP was 90/74 mm Hg, and her heart rate was still

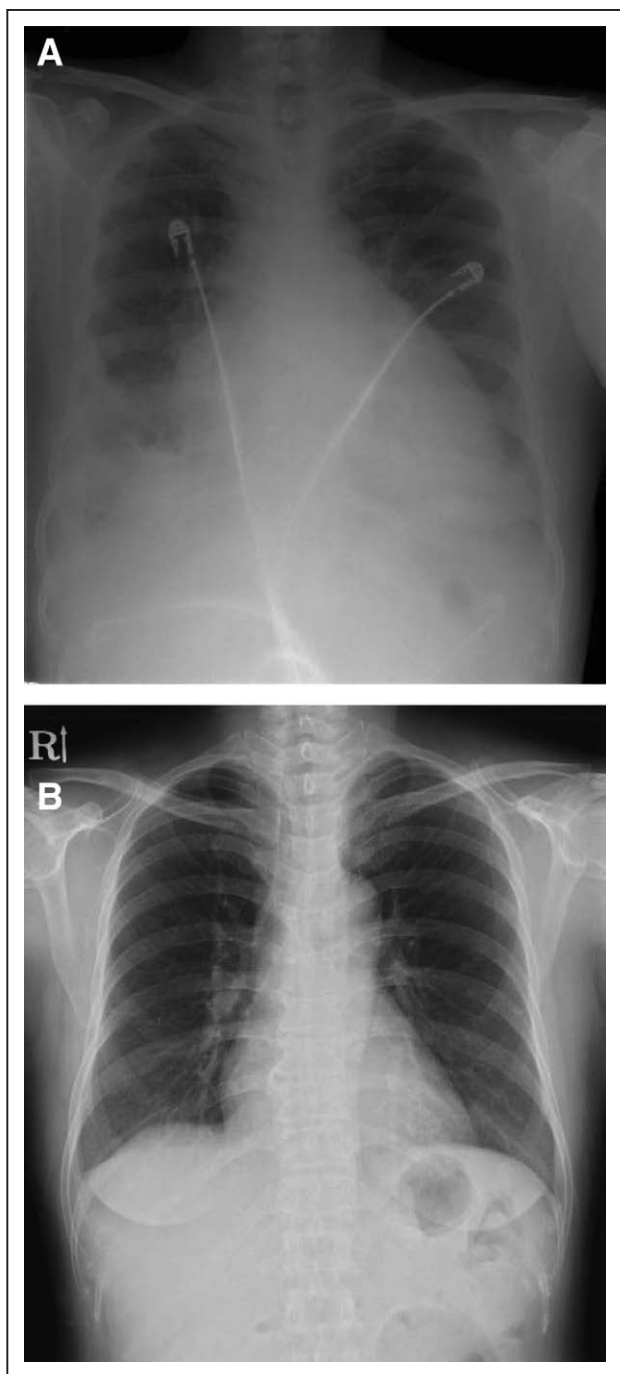


Figure 1. A, Initial chest x-ray (Chest PA). B, Chest x-ray at 2 y.

high at 107 bpm. Medication at discharge was typical for heart failure management: carvedilol 6.25 mg BID, captopril 12.5 mg TID, and furosemide 40 mg QD. As you can see, we had started β -blocker treatment without α -blockade.

Was It Possible to Suspect Pheochromocytoma?

Dr Lee: A point of interest is how this patient was safe with inotropics. We all know that sympathomimetics may stimulate catecholamines, which may be harmful to the patient. However, desensitization of the cardiovascular system to catecholamines after long-term exposure to high circulating levels may contribute to a relatively normal BP and blunted

response to sympathomimetics.¹ Regardless, with this presentation, could you suspect pheochromocytoma in this patient?

Professor Dominiczak: Clearly, difficult; as you told us at the beginning, pheochromocytoma is a great mimic. I think you discovered this patient at a time when this great mimicry was already advanced; I presume this pheochromocytoma had been present for a while, and the excessive catecholamines caused destructive changes of cardiomyocytes leading to dilated cardiomyopathy. As the BP was completely normal or low, you did not measure the catecholamine levels.

Case Continues

At the outpatient clinic, the patient's BP and heart rate normalized and stayed stable for 2 years on carvedilol 6.25 mg BID, losartan 50 mg QD, and torasemide 5 mg QD. In the second year, her BP started to increase to 150/100 mmHg, and long-acting nifedipine was added. Also, blood sugar levels remained marginally high at fasting blood glucose 180 mg/dL and HbA1c 6.8% despite lifestyle modifications; therefore, metformin was added. With addition of medication, BP and blood glucose levels were controlled once more.

ECG and chest x-ray were conducted at the 2-year follow-up. There is diffuse T inversion on the ECG (Figure 2B), but her chest x-ray shows improvements with disappearance of cardiomegaly and pulmonary congestion (Figure 1B). Follow-up echocardiography was done and left ventricular cavity size was normalized, with an end-systolic dimension of 24 mm and an end-diastolic dimension of 46 mm. Ejection fraction recovered from 28% to 73%. Secondary mitral regurgitation disappeared, and ejection fraction was normalized, but apical akinesia was still present (Movies S5 through S8).

At third year of follow-up at the outpatient clinic, her BP, heart rate, and blood sugar levels started to slowly rise. BP medication was changed to single-pill combination of amlodipine/valsartan 5 mg/160 mg. Sitagliptin was added, and later, the dose was increased. Carvedilol was initially discontinued because of concerns that it might aggravate hyperglycemia, but then, BP and heart rate rose, and bisoprolol 2.5 mg QD was added again.

BP was stable with medication, but blood glucose levels continued to rise. In the fifth year, her glucose levels started increasing steeply, and HbA1c suddenly rose to 9.3%. Glimepiride was added. After 3 months, HbA1c level decreased once more to 7.3%. During this time, BP was stable.

At 5 years, we performed another follow-up. Her ECG was totally normalized (Figure 2C), and the chest x-ray was normal. Echocardiography continued to show normal left ventricular size and systolic function, and apical akinesia was also resolved (Movies S9 through S12).

At the sixth year of follow-up, BP started rising once more to 150/90 mmHg. She was on amlodipine, valsartan, and carvedilol. Thiazide and spironolactone were added, and the β -blocker dosage of carvedilol was increased to 25 mg twice daily. Meanwhile, HbA1c levels were stable on metformin, sitagliptin, and glipizide but rather high at 7.7%.

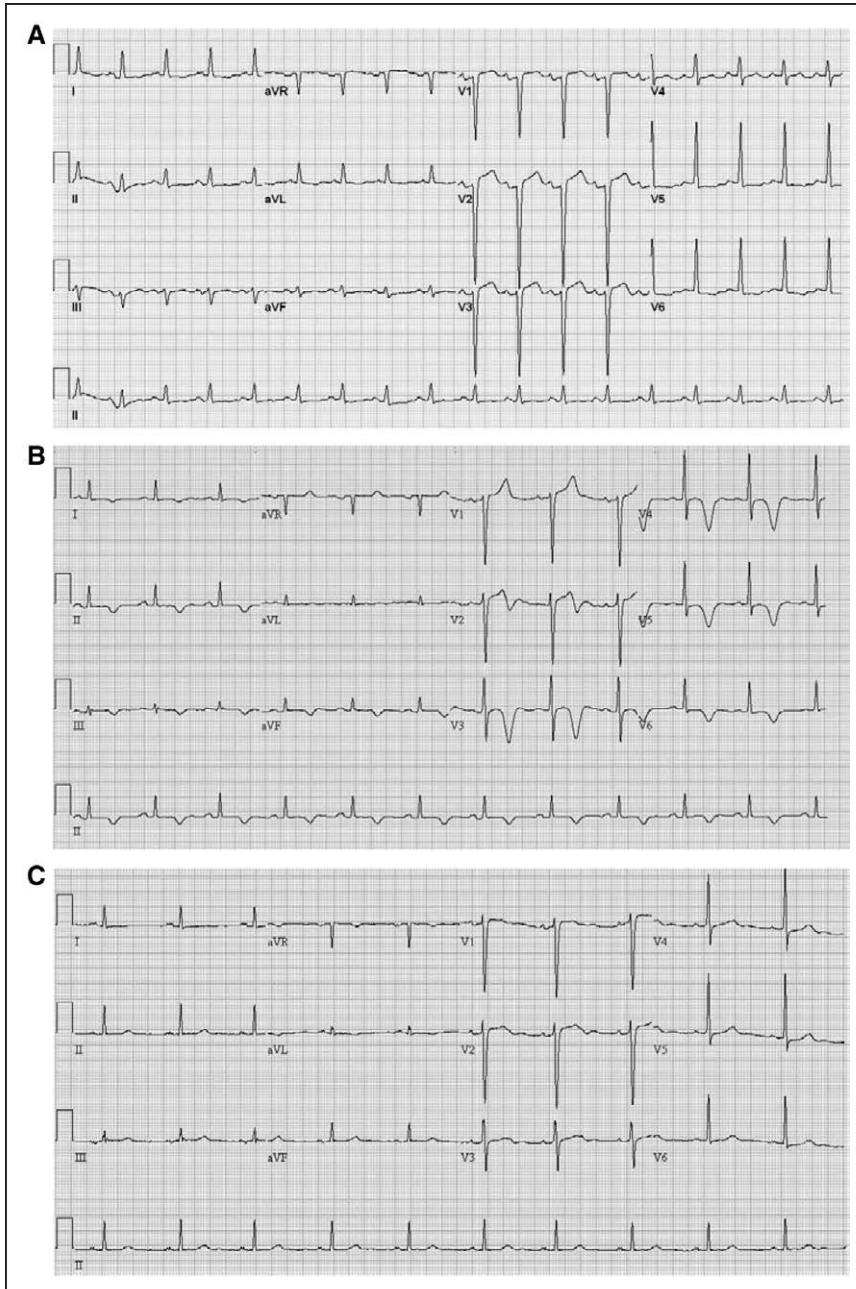


Figure 2. A, Initial ECG. B, ECG at 2 y. C, ECG at 5 y.

Hypertension in Pheochromocytoma

As you can see, her BP continued to rise but was maintained under control with addition of medication, making it hard to suspect secondary hypertension. When screening for secondary hypertension, pheochromocytoma is always one of the first things to rule out. However, pheochromocytoma is an uncommon cause of secondary hypertension. Pheochromocytoma is diagnosed in 0.2% of all hypertension patients, and even in resistant hypertension, the prevalence is only 1%.² On the contrary, most of the pheochromocytoma patients show hypertension, either sustained or paroxysmal.

There are subtle differences in the pattern of hypertension based on the main secreted catecholamine. In the nor-epinephrine-dominant type, peripheral vascular resistance is mainly increased, resulting in increase of both systolic

BP and diastolic BP, and patients usually show sustained hypertension. However, in the epinephrine dominant type, cardiac output is mainly increased and episodic symptoms are more common, and systolic BP is increased while there is no major effect on diastolic BP because of β -2-adrenoceptor-mediated vasodilator actions.³ In the majority, paroxysmal hypertension occurs at least weekly and generally lasts from several minutes to 1 hour.⁴ In the rare dopamine-dominant types, patients often show normotension or even hypotension.

Time to time at the outpatient clinic, our patient complained of headache. She did not measure home BP, and every time she visited the clinic, BPs were within reference ranges. It was not possible to determine whether headaches were an episodic symptom of pheochromocytoma.

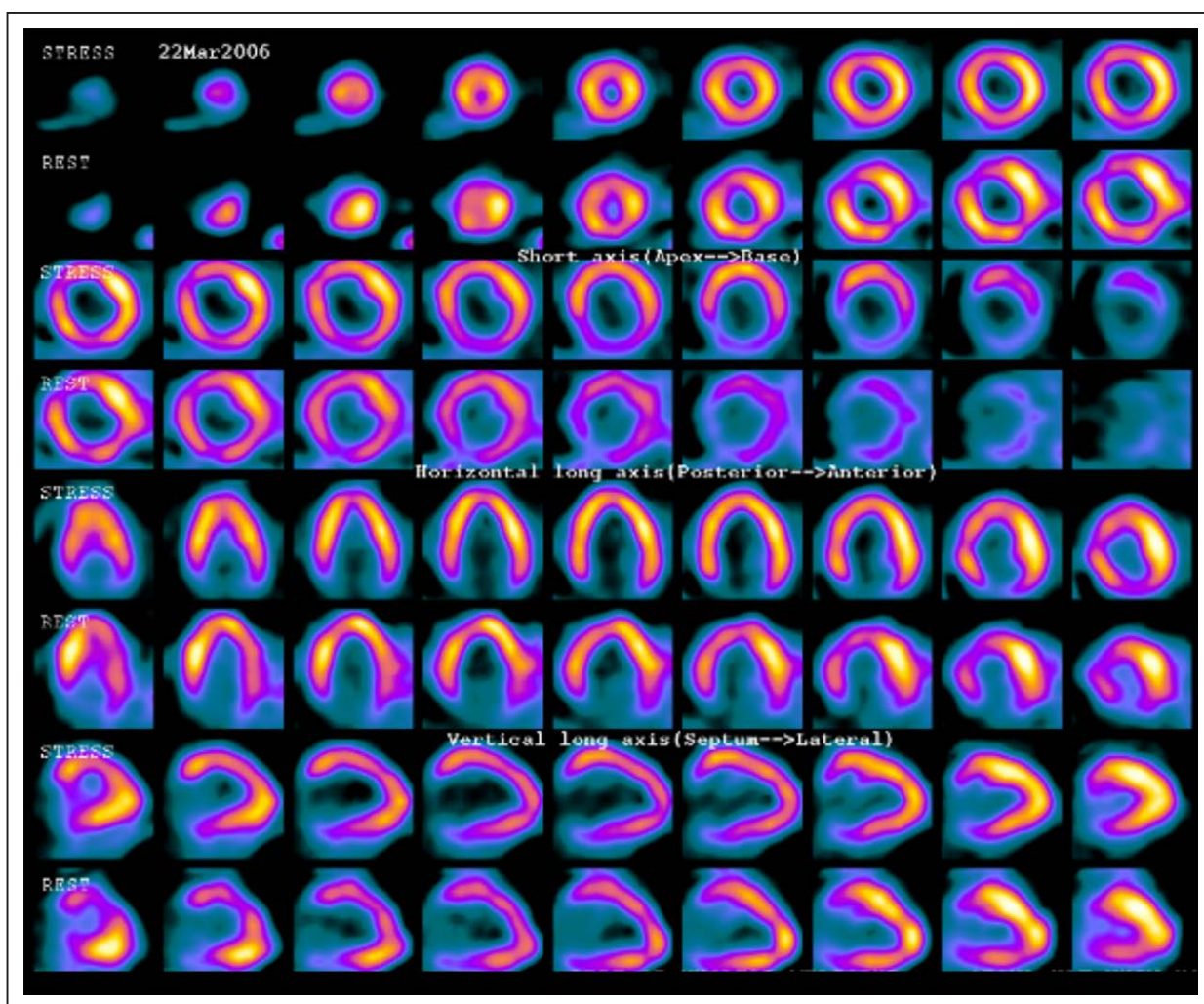


Figure 3. Myocardial single positron emission computed tomography.

A notable point in the case is that the patient continued to receive β -blockers to control BP and heart rate, in the absence of α -blockade. Theoretically, in pheochromocytoma, β -blockers should never be initiated until there is sufficient α -adrenoceptor blockade, because the inhibition of β -2-adrenoceptor-mediated vasodilatory actions may cause enhanced vasoconstrictor responses leading to further increase in BP. Thus, cardioselective β -blockers are preferred. Carvedilol's α -blocking potential is much less than its β -blocking efficacy.

Discovering Pheochromocytoma

At the seventh year of follow-up, glycemic levels started to deteriorate despite intensification of oral hypoglycemic agents. Carvedilol was discontinued because of concern of its aggravating hyperglycemic effects. In the eighth year, despite full dose of metformin, sitagliptin, and sulfonylurea, HbA1c rose to 9.4%, and the endocrinology department was consulted for a second opinion. On their recommendation, insulin was started (Figure 4). BP rose to 144/84 mmHg, and heart rate rose to 103 bpm, after discontinuation of β -blocker.

At that time, the urinalysis and microscopy, performed as part of her diabetes mellitus follow-up, showed appearance

of albuminuria, and ominously, microscopic hematuria at 10 to 19/high-power field. For further work up of intermittent microscopic hematuria, urine cytology was done and found to be negative, and abdomen computed tomography was done. On the abdominal computed tomography, unexpectedly, a huge mass at the right adrenal gland was discovered (Figure 5). The lobulating mass was around 7×7 cm and showed good enhancement with internal cystic change and suspicious focal hemorrhage, which was consistent with pheochromocytoma.

Hormone tests were done, and serum metanephrine and normetanephrine levels were elevated, as well as urine catecholamine levels. Renin and aldosterone levels were also elevated. Whole-body positron emission tomography showed a hypermetabolic mass in the right adrenal gland, and otherwise, no distant metastasis.

Thus, the patient was diagnosed with pheochromocytoma. Hormone evaluation showed greatly elevated serum and urine catecholamines (Table). Especially, metanephrine and epinephrine levels were elevated, indicating a predominantly adrenalin-secreting type of pheochromocytoma. α -Blockade with doxazosin at 2 mg BID was started, and she was referred for surgery.

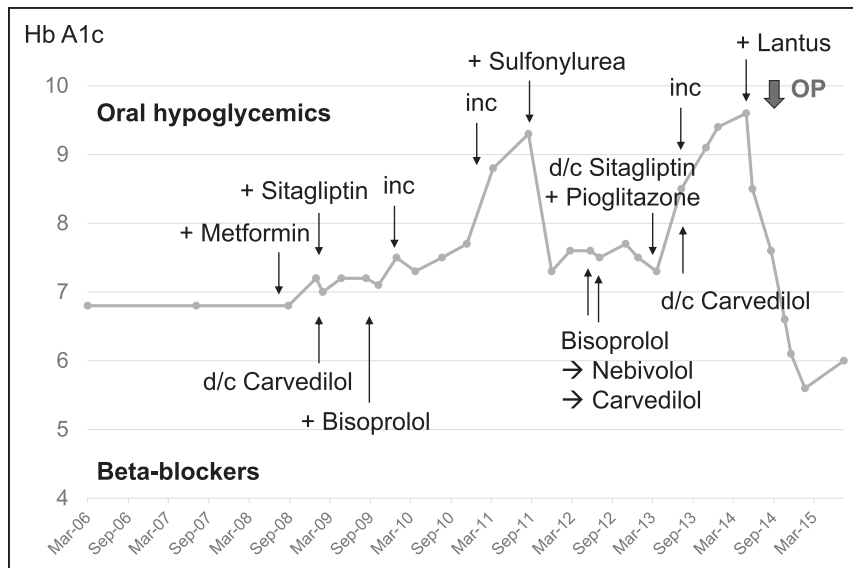


Figure 4. Hemoglobin A1c (HbA1c) levels during follow-up and concomitant medication with oral hypoglycemic and β -blockers. d/c indicates discontinued; inc, increased dose; and OP, operation (resection of pheochromocytoma).

Discussion Continues

Dr Lee: In her clinical course, after the first episode of heart failure, heart function normalized on echocardiography follow-up. BP and heart rate were controlled marginally on oral medication and responded to β -blockers. Diabetes mellitus progressed out of control despite full medication. After 9 years of follow-up, pheochromocytoma was incidentally diagnosed after computer tomography because of microscopic hematuria. At this point, I hope to ask your opinion, at what time could I have diagnosed pheochromocytoma earlier during 9-year follow-up?

Professor Dominiczak: I think it is difficult in this case because she did not really have prominent hypertension until late. My question is, during observation of this patient, have you ever done ambulatory BP monitoring? Or home BP monitoring? This could have picked up things earlier.

Dr Lee: No, I did not think of doing ambulatory BP and that is a good point, because she was on more than the usual 2 medications to control BP.

Dr Jennings: I do not know when you could have made this diagnosis. You had to get lucky, I think. It is interesting, reflecting on the pharmacology of carvedilol that she was not hypertensive until you improved her ventricular function to the point that she could sustain an elevated BP. It was fortunate that a drug, which is predominantly a β -blocker with a little bit of α -blockade, did not increase her BP further because she was predominantly secreting adrenalin. It has been a course that could have been different, if it had been a different kind of pheochromocytoma.

Dr Siddique: Two questions. You have had a lot of tests done but what was her fundoscopy like initially and on subsequent examinations? Also, at the initial emergency room tests, she showed elevated prothrombin time (INR) of 1.59; was it investigated?

Dr Lee: During her follow-up, I did not think she was the typical hypertension or hypertensive heart failure patient, and I did not send her for retinal examination. Initial INR was only mildly elevated at 1.59, and I thought this was part of

congestive hepatomegaly. Prothrombin time was normalized after discharge.

Professor Cho: On her second examination at 2 years, there is a Q-wave inversion in ECG, and echocardiography shows apical aneurysm. There seems to be enough reason to perform a coronary angiography because she has diabetes mellitus and hypertension. Did she ever have angina symptoms, and did you check cardiac enzymes or ever perform the coronary angiography?

Dr Lee: Good question. We often perform coronary angiography at the first presentation to investigate heart failure cause, but in this case, the initial cardiac enzymes were completely normal. Also, her clinical response to heart failure management was rapid. SPECT did not show signs of hypoperfusion. On the basis of these 2 findings, I ruled out the possibility of a coronary artery disease.

Professor Cho: Sometimes pheochromocytoma produce cortisol. During her course, did she ever develop any hypokalemia?

Dr Lee: No, as I used thiazide diuretics, I routinely checked electrolytes, but she did not show hypokalemia or other derangements.

Case Resolution

It took 9 years from first meeting this patient to the final diagnosis of pheochromocytoma. Diabetes mellitus progressed out of control during follow-up, but after the operation, her blood sugar levels totally normalized without any medication. Hypertension also totally disappeared.

At this point, I would like to talk about diabetes mellitus in pheochromocytoma. Pheochromocytoma is one of the endocrine disorders with the highest prevalence of diabetes mellitus at 33% and impaired glucose tolerance at 50%.⁵ For majority of patients, hypoglycemia is present but usually takes a milder course. The adrenaline-dominant type has higher affinity for β -receptor and is, therefore, more potent in producing hyperglycemia. β -receptors stimulate gluconeogenesis and α -2 receptors decrease insulin release, which are the main mechanisms of pheochromocytoma-associated

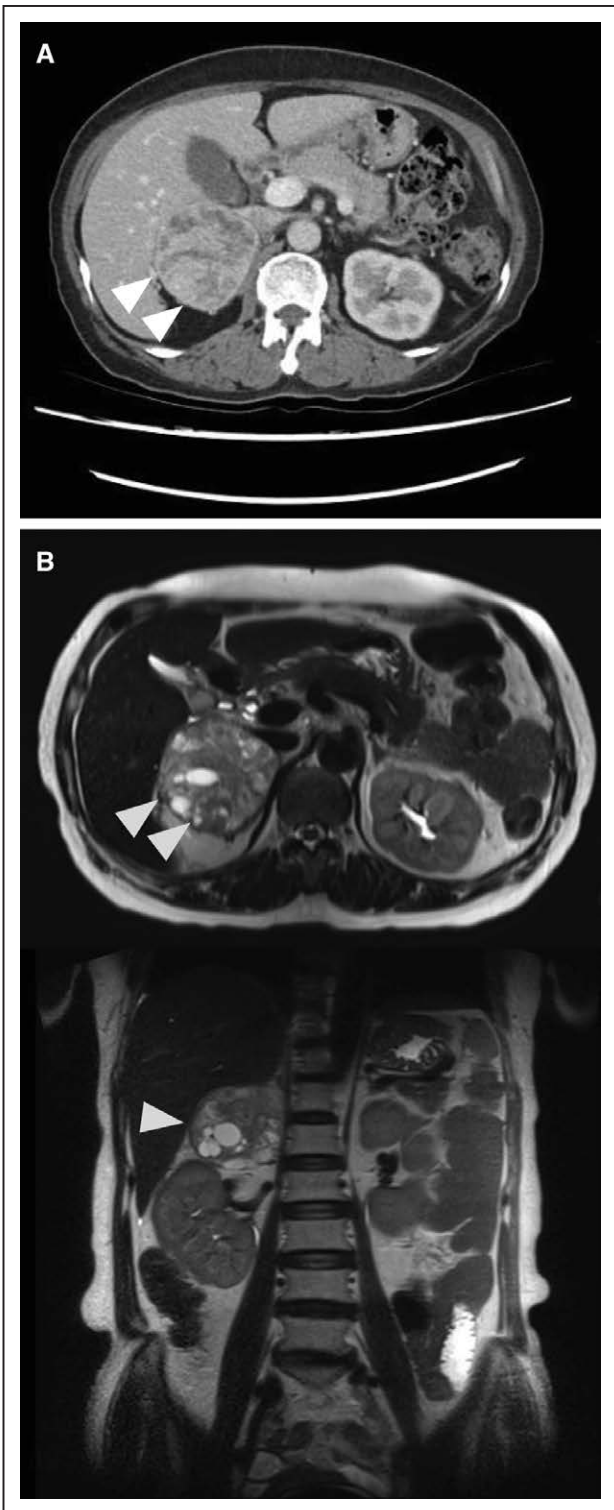


Figure 5. Abdomen imaging at 8 y. **A**, Computed tomography. **B**, Magnetic resonance imaging.

hyperglycemia. During her course, when her HbA1c rose to 9.3%, I added sulfonylurea at only one tablet per day, and her HbA1c level decreased by 2 points. This is unusual, because usually, sulfonylurea only decreases HbA1c by 1%. This may have been related to rejuvenation of insulin release from the basal cell.

Table. Hormone Evaluation (Year 8)

Hormones	Measured Values	Normal Range
Serum		
Metanephrine, pg/mL	>20 000	90–130
Normetanephrine, pg/mL	16 877	100–2300
24-h urine		
Epinephrine, μg	1219.4	0–20
Norepinephrine, μg	490.9	15–80
Dopamine, μg	174.7	65–400
Metanephrine, μg	12 326.2	52–341
Normetanephrine, μg	4078.6	88–444
Urine VMA, $\mu\text{g}/\text{mg Cr}$	25.7 mg, 28.9	2–7 mg, 0–7
Renin, $\text{ng}\cdot\text{mL}^{-1}\cdot\text{h}^{-1}$	26.7	1–2.5
Aldosterone, ng/dL	23.5	3–16
Cortisol(S), $\mu\text{g}/\text{dL}$	21.4	5–25
DHEA-S, ng/mL	361	350–4300

DHEA-S indicates dehydroepiandrosterone sulfate; and VMA, vanillylmandelic acid.

After diagnosing pheochromocytoma, we started α -blockade with doxazosin and supplied sufficiently massive fluid resuscitation of 6 L per day 1 day before the operation. Because the patient usually has volume constriction, hydration is important to prevent hypotensive episodes during the operation.

Regarding preoperative α -blocking, there is still debate over whether the nonselective α -blocker phenoxybenzamine is better or the α 1-selective blocker doxazosin is better.⁶ One good point of phenoxybenzamine is better BP control, but phenoxybenzamine is not a familiar antihypertensive agent. On the contrary, doxazosin is familiar and is known to be associated with less pronounced BP fluctuation during surgery.⁷ In this case, we used doxazosin, but current standard of BP control for pheochromocytoma in my hospital is phenoxybenzamine.

The pathology report for the resected right adrenal mass showed pheochromocytoma with portions of malignant change (Figure 6). After surgical removal of pheochromocytoma, diabetes mellitus and hypertension completely disappeared, and the patient is off medication.

Final Discussion Points

Dr Lee: I would like to ask the audience's opinion on what the adequate preoperative α -blockade strategy is between phenoxybenzamine and doxazosin?

Professor Dominiczak: In our center, we would have used phenoxybenzamine because that is how it has always been done, but I do not think there is any evidence that one is truly better than the other. It is good to lower BP preoperatively as you did. Maybe it does not matter which drug is used, it is important to control BP carefully during surgery to avoid any big BP variations, both up and down.

There is one additional question that just came to my mind. Was she ever pregnant before? There have been previous reports that occasionally pheochromocytoma comes to light

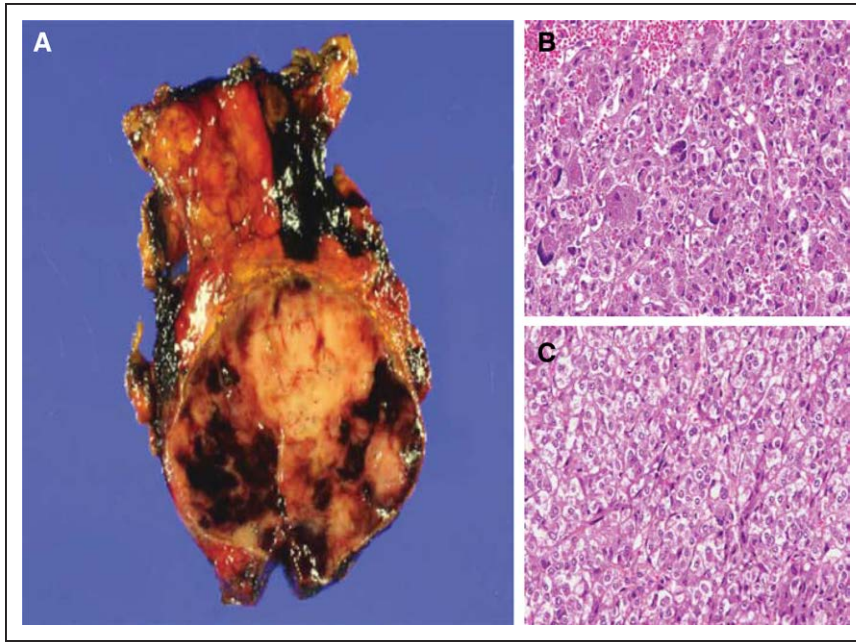


Figure 6. Pathology. **A**, Gross specimen. **B**, Malignant portion of the mass showing profound nuclear polymorphism and hyperchromasia and absence of regular nest pattern. **C**, Benign portion of the mass showing round nuclei and trabecular shaped cell nests.

during pregnancy, especially if there are any procedures such as a cesarean section.

Dr Lee: No. She had no experience of pregnancy. One year before heart failure elevation, she had surgery for hemorrhoid under local anesthesia, and there were no problems.

Summary

Final diagnosis was adrenalin dominantly secreting type of pheochromocytoma, which caused transient heart failure and diabetes mellitus. Through this conference, I hope you will keep in mind that pheochromocytoma has multiple faces and to consider this possibility in unusual cases.

Disclosures

None.

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