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

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The following case was presented 26 September 2016 as part of the Clinical-Pathological conference chaired by Anna F. Dominiczak and Rhian M. Touyz at the 26th Scientific Meeting of the International Society of Hypertension. Hyun-Jung Lee presented the case and the discussion was led by Hae-Young Lee.

Case Introduction

A 47-year-old female visited the emergency room in March 2006. Her main complaint was dyspnea, which began two months prior. She was a previously healthy woman, but after upper respiratory infection two months before, she developed symptoms of cough, myalgia, epigastric pain, and dyspnea of NIHA 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 prior to 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, non-smoker 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 mmHg. Heart rate was slightly elevated at 113 beats per minute and her breathing was rather fast at 22 times per minute. Body temperature and oxygen saturation were normal. Her height was 161 centimeters and her weight was 67 kilograms; she was overweight.

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 units per liter and alanine transaminase 1,868 units per liter. Prothrombin time (INR) was elevated at 1.59 and her urine was rather concentrated and albuminuria was 2 positive. B-natriuretic peptide (BNP) level was 2,002 picograms per 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 electrocardiogram (ECG) showed sinus tachycardia with ST elevation at V1 to V3 and ST depression at V6 suggesting a left ventricular hypertrophy (Figure 2). Her initial echocardiogram was as follows; she had dilated LV cavity with an end-systolic dimension of 61 millimeters and an end-diastolic dimension of 72 millimeters and wall thickness was normal. There was global hypokinesia with secondary mitral regurgitation (MR) due to tethering, and ejection fraction was decreased at 28% (Video 1-4).

A myocardial SPECT 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 ACE inhibitor and beta blocker. She was discharged after 1 week; at time of discharge, her BP was 90/74 mmHg and her heart rate was still high at 107 BPM. Medication at discharge was typical for heart failure management: carvedilol 6.25 mg twice daily, captopril 12.5 mg three times daily, and furosemide 40 mg daily. As you can see, we had started beta-blocker treatment without alpha blockade.

Was it Possible to Suspect Pheochromocytoma?

Dr. Hae-Young Lee: A point of interest is how this patient was safe with inotropics. We all know that sympathomimetics may stimulate catecholamines, which may be very 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 sympathomimetics¹. Regardless, with this presentation, could you suspect pheochromocytoma in this patient?

Prof. Anna Dominiczak: Clearly, very 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 very advanced; I presume this pheochromocytoma had been present for quite a while and the excessive catecholamines caused destructive changes of cardiomyocytes leading to dilated cardiomyopathy. As the BP was completely normal or low, you didn't measure the catecholamine levels.

The Case Continues

At the outpatient clinic, the patient's BP and heart rate normalized and stayed stable for two years on carvedilol 6.25 mg twice daily, losartan 50 mg daily and torasemide 5 mg daily. In the second year, her BP started to increase to 150/100 and long acting nifedipine GITS 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 two 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 LV cavity size was normalized, with an end-systolic dimension of 24 millimeters and an end-diastolic dimension of 46 millimeters. Ejection fraction recovered from 28% to 73%. Secondary MR disappeared and ejection fraction was normalized but apical akinesia was still present (Video 5-8).

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 5mg/160mg. Sitagliptin was added and later the dose was increased. Carvedilol was initially discontinued due to concerns that it might aggravate hyperglycemia, but then BP and heart rate rose and bisoprolol 2.5 mg daily was added again.

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

At five 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 (Video 9-12).

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 beta blocker dosage of carvedilol was increased to 25 mg twice daily. Meanwhile, HbA_{1c} levels were stable on metformin, sitagliptin and glipizide but rather high at 7.7%.

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 other hand, 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 norepinephrine dominant type, peripheral vascular resistance is mainly increased, resulting in increase of both SBP and DBP, and patients usually show sustained hypertension. However, in the epinephrine dominant type, cardiac output is mainly increased and episodic symptoms are more common, and SBP is increased while there is no major effect on DBP due to beta 2-adrenoceptor-mediated vasodilator actions³. In the majority, paroxysmal

hypertension occurs at least weekly and generally lasts from several minutes to one hour⁴. 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, blood pressures were within reference ranges. It was not possible to determine whether headaches were an episodic symptom of pheochromocytoma.

A notable point in the case is that the patient continued to receive beta blockers to control BP and heart rate, in the absence of alpha blockade. Theoretically, in pheochromocytoma, beta blockers should never be initiated until there is sufficient alpha-adrenoceptor blockade, because the inhibition of beta 2-adrenoceptor mediated vasodilatory actions may cause enhanced vasoconstrictor responses leading to further increase in BP. Thus, cardioselective beta blockers are preferred. Carvedilol's alpha blocking potential is much less than its beta 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 due to 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 5). BP rose to 144 / 84 mmHg, and heart rate rose to 103 bpm, after discontinuation of beta blocker.

At that time, the urinalysis and microscopy, performed as part of her diabetes follow-up, showed appearance of albuminuria, and ominously, microscopic hematuria at 10-19/HPF. For further work up of intermittent microscopic hematuria, urine cytology was done and found to be negative, and abdomen computed tomography (CT) was done. On the abdominal CT, unexpectedly, a huge mass at the right adrenal gland was discovered (Figure 4). The lobulating mass was around 7 x 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 PET 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 1). Especially, metanephrine and epinephrine levels were elevated, indicating a predominantly adrenalin secreting type of pheochromocytoma. Alpha blockade with doxazosin at 2 mg twice daily was started, and she was referred for surgery.

Discussion continues

Dr. Hae-Young 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 beta blockers. Diabetes mellitus progressed out of control despite full medication. After nine years of follow up, pheochromocytoma was incidentally diagnosed after computer tomography due to microscopic hematuria. At this point, I hope to ask your opinion, at what time could I have diagnosed pheochromocytoma earlier during nine years follow up?

Prof. Anna Dominiczak: I think it is very difficult in this case because she did not really have prominent hypertension until very 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. Hae-Young Lee: No, I did not think of doing ambulatory BP, and that is a good point, because she was on more than the usual two medications to control BP.

Prof. Garry Jennings: I do not know when you could have made this diagnosis. You had to get lucky, I think. It's 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 beta blocker with a little bit of alpha blockade, did not increase her BP further because she was predominantly secreting adrenalin. It has been a course which could have been very different, if it had been a different kind of pheochromocytoma.

Dr. Saula 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. Hae-Young 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.

Dr. Eun Joo Cho: On her second examination at two 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 and hypertension. Did she ever have angina symptoms, and did you check cardiac enzymes or ever perform the coronary angiography?

Dr. Hae-Young Lee: Very good question. We often perform coronary angiography at the first presentation to investigate heart failure etiology, but in this case, the initial cardiac enzymes were completely normal. Also, her clinical response to heart failure

management was quite rapid. SPECT did not show signs of hypoperfusion. Based on these two findings, I ruled out the possibility of a coronary artery disease.

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

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

Case Resolution

It took nine years from first meeting this patient to the final diagnosis of pheochromocytoma. Diabetes 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 in pheochromocytoma. Pheochromocytoma is one of the endocrine disorders with the highest prevalence of diabetes 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 beta receptor and is therefore more potent in producing hyperglycemia. Beta receptors stimulate gluconeogenesis and alpha-2 receptors decrease insulin release, which are the main mechanisms of pheochromocytoma associated 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 two 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.

After diagnosing pheochromocytoma, we started alpha blockade with doxazosin, and supplied sufficiently massive fluid resuscitation of six liters per day one day before the operation. Because the patient usually has volume constriction, hydration is very important to prevent hypotensive episodes during the operation.

Regarding pre-operative alpha blocking, there is still debate over whether the nonselective alpha blocker phenoxybenzamine is better or the alpha1-selective blocker doxazosin is better⁶. One good point of phenoxybenzamine is better BP control, but phenoxybenzamine is not a familiar antihypertensive agent. On the other hand, doxazosin is familiar, and is known to be associated with less pronounced BP fluctuation during surgery⁷. 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 and hypertension completely disappeared and the patient is off medication.

Final Discussion Points

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

Prof. 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 quite good to lower BP preoperatively as you did. Maybe it does not matter which drug is used, it is important to control BP very 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 during pregnancy, especially if there are any procedures such as a cesarean section.

Hae-Young 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

The authors have no conflicts of interest to disclose.

Sources of Funding

None.

Tables

Table 1. Hormone evaluation (Year 8)

Hormones	Measured values	Normal Range
Serum		
Metanephrine	>20,000 pg/mL	90-130 pg/mL
Normetanephrine	16,877 pg/mL	100-2300 pg/mL
24 hour urine		
Epinephrine	1,219.4 ug	0-20 ug
Norepinephrine	490.9 ug	15-80 ug
Dopamine	174.7 ug	65-400 ug
Metanephrine	12,326.2 ug	52-341 ug
Normetanephrine	4,078.6 ug	88-444 ug
Urine VMA	25.7 mg, 28.9 ug/mg Cr	2-7 mg, 0-7 ug/mg Cr
Renin	26.7 ng/mL/hr	1-2.5 ng/mL/hr
Aldosterone	23.5 ng/dL	3-16 ng/dL
Cortisol(S)	21.4 ug/dL	5-25 ug/dL
DHEA-S	361 ng/mL	350-4300 ng/mL

Figures

Figure 1. (A) Initial chest X-ray (Chest PA). (B) Chest PA at 2 years.

Figure 2. (A) Initial electrocardiogram (ECG). (B) ECG at 2 years. (C) ECG at 5 years.

Figure 3. Myocardial SPECT

Figure 4. Abdomen imaging at 8 years. (A) CT. (B) MRI.

Figure 5. Hemoglobin A₁C levels during follow up, and concomitant medication with oral hypoglycemic and beta blockers.

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.

Videos

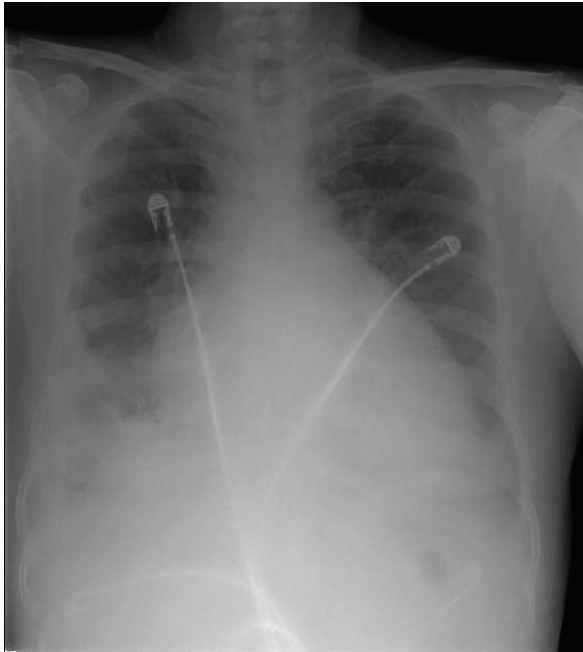
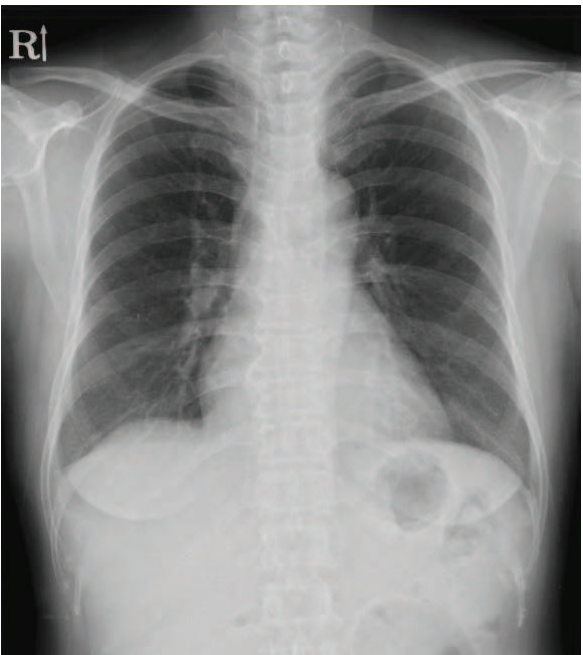
Video 1-4. Initial echocardiogram.

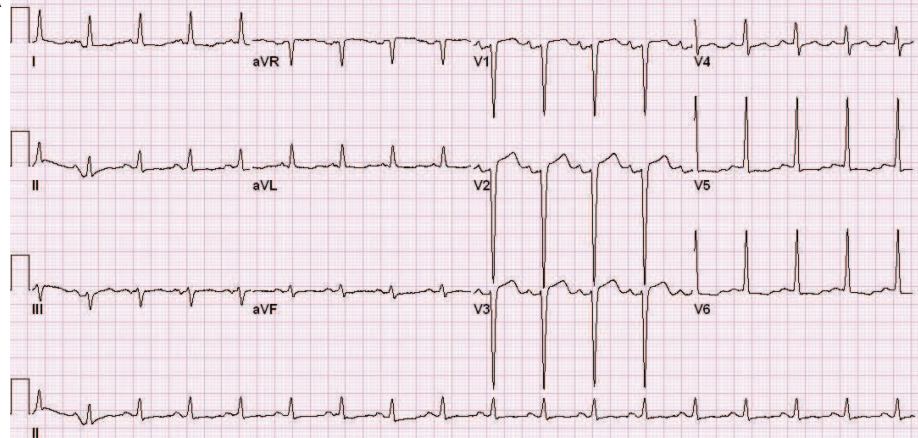
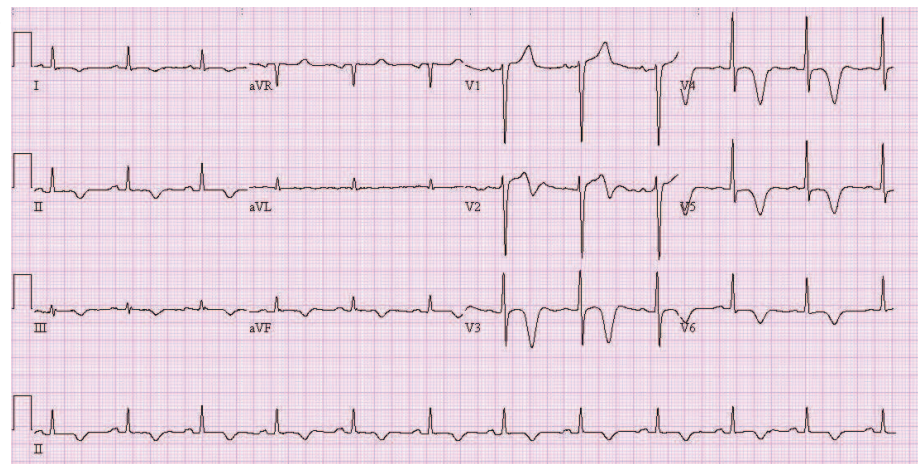
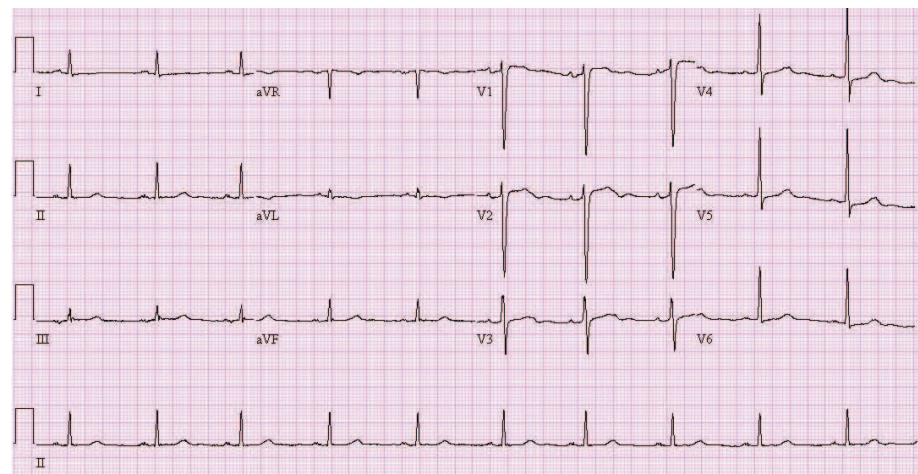
Video 5-8. Echocardiogram at 2 years.

Video 9-12. Echocardiogram at 5 years.

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Short axis (Apex-->Base)

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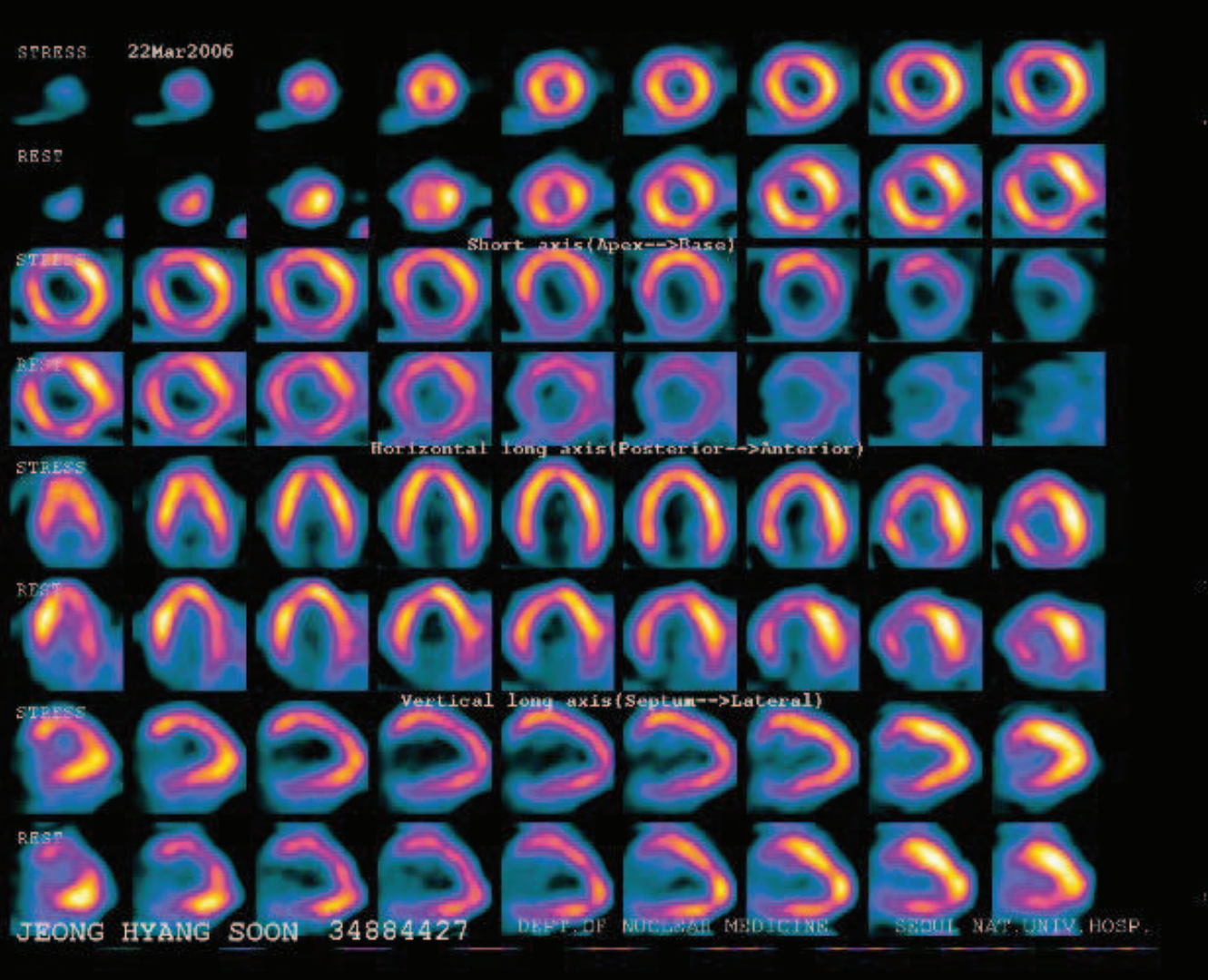
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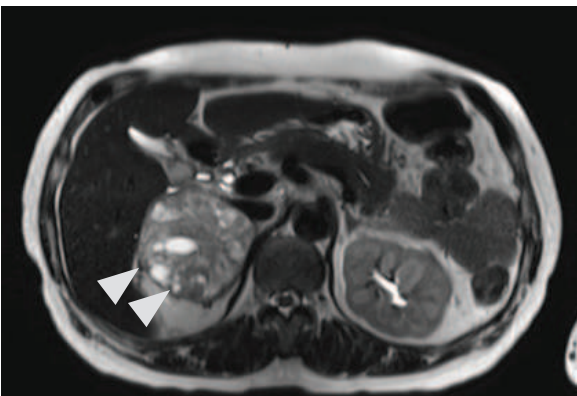
Horizontal long axis (Posterior-->Anterior)

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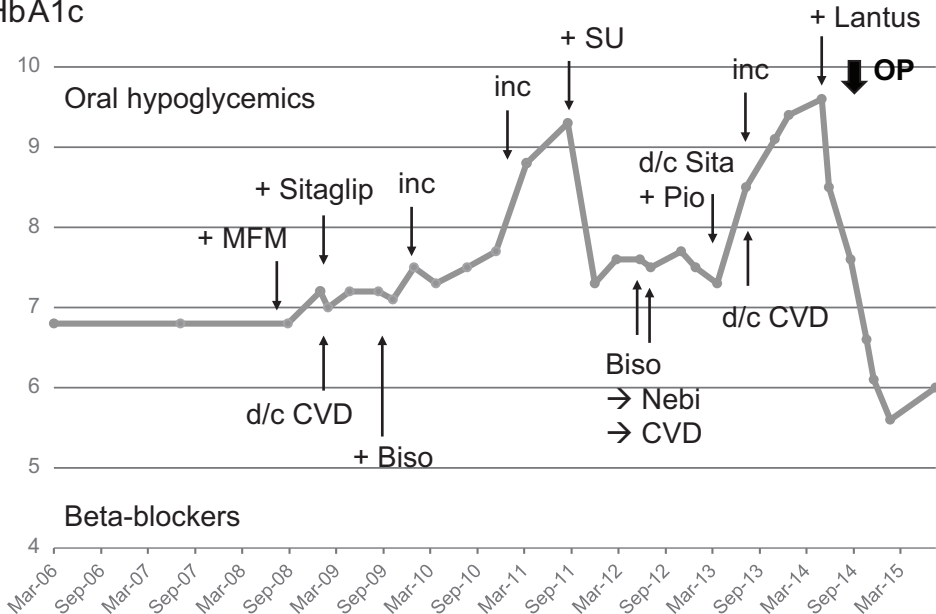
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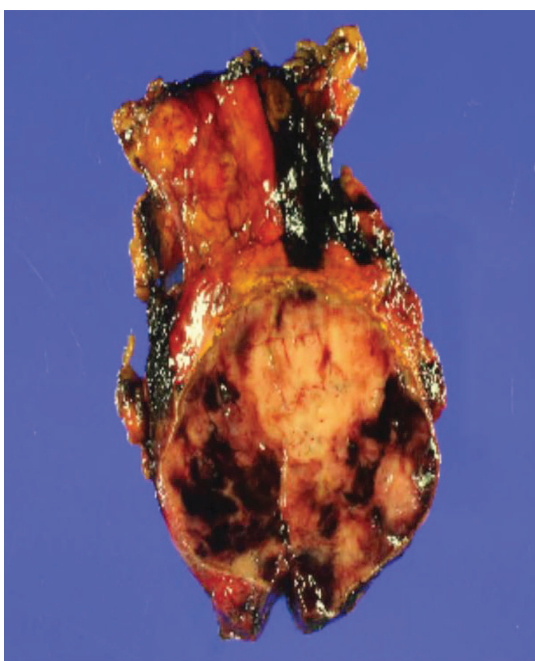
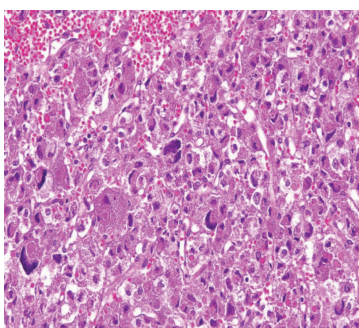
Vertical long axis (Septum-->Lateral)



A**B**

HbA1c



A**B****C**