Young male with heart failure and negative angiogram

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Abstract

A young previously well male presented with features of acute coronary syndrome and heart failure. ECG showed inferior ST elevations but his cardiac markers and angiogram was negative. He was found to have a large abdominal paraganglioma with normal adrenal glands. He had a successful excision of the tumor and is now under life- long surveillance. He is awaiting genetic testing.

Key works- Paraganglioma, Negative angiogram

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Case

Mr.PW, a 32 year old previously well male, got admitted to the local hospital with sudden onset, severe tightening chest pain. Examination revealed decompensated congestive cardiac failure with no signs of pericarditis. An acute cardiac event was suspected. ECG showed ST segment elevations in the inferior leads. Interestingly, troponin I level was negative. Following stabilization, he was immediately transferred to the cardiology unit at Teaching Hospital Kurunegala.

PW was a young fit self- employed gentlemen with a good exercise tolerance. There was no significant family history of cardiovascular disease and he was a non-smoker. He was treated with Intravenous (IV) GTN infusion, IV Frusemide along with antiplatelets. Chest X –ray revealed evidence of pulmonary odema without cardiomegaly. Echocardiogram revealed ejection fraction of 35% with marked hypokinesia of inferior and posterior walls. Once stabilized, an elective coronary angiogram was performed. During the procedure, his condition deteriorated again as the blood pressure shot up to 220/120 mmHg with ECG revealing a stain pattern. Surprisingly, the angiogram was negative with none of the coronary arteries demonstrating any blockage. His blood pressure remained elevated.

He was put on antihypertensives cautiously: beta-blockers had been avoided, and was transferred to the cardiology unit Colombo for further management. He was referred to the Endocrinology team to be evaluated as a young hypertensive patient.

On specific questioning, he revealed that he experienced episodes of short lasting palpitations, headache and excessive sweating over the last 6-7 months. These episodes occurred without a specific precipitating event. He did not have a history of anxiety disorder and was not on any drugs which could cause similar symptoms. There were no evidence of muscle weakness, easy bruising, factures or recent change in his appearance. He consumed alcohol occasionally. There was no family history of hormone disorders, high calcium, brain tumors, adrenal tumors or early onset hypertension. He was a father of one child and managed his own grocery shop.

On examination, he was thin built with a body mass index (BMI) of 20.5 kg/m2. His height was similar to his sibling and did not have any marfanoid body habitus, skin rashes or skin or mucosal tags/growths. He had a small, none-tender diffuse goiter without cervical lymphadenopathy .He had   sinus

tachycardia with a pulse rate of 110 beats/min and a blood pressure of 180/110 mmHg (lying and standing) without no difference in the arms. No masses were palpable in the abdomen and there were no abdominal or thoracic bruit. There was no cardiomegaly or chronic hypertensive retinopathy indicating an abrupt onset of hypertension. There were no cardiac murmurs. Further examination was also normal. PW did not have a family history of Pheochromocytoma and evidence for other endocrinopathies were not present. Features of Von Hippel Lindau syndrome, such as cerebellar hemangioblastoma, retinal angiomas, renal cell carcinoma, and islet cell tumours were not clinically apparent in our patient, neither did he have neurofibromas or Café au lait patches.

Basic testing including renal functions and serum electrolytes were normal without any hypokalemia. Ultrasound scan of the abdomen with renal Doppler was normal without any renal, adrenal structural abnormalities or renal artery stenosis. Due to episodic spells and negative angiography, pheochromocytoma

had to be excluded. Though urine fractionated metanephrines/plasma metanephrines could be regarded as the best test to investigate this, since it was not available in the government sector and because of the cost, the patient underwent urine 24 hour Vanillylmandelic Acid (VMA) testing. VMA showed an elevated level of 27.2 ng/ml (1-11 ng/ml) which was confirmed by a second reading, at 39.6 ng/ml.

Localizing studies were done and CT scan of the abdomen showed normal bilateral adrenal glands. However, there was a 2.6cm ×3.3 cm× 2.3 cm size, peripherally enhancing retroperitoneal paraaortic mass on the right side of the aorta, at the level of the renal artery behind the head of the pancreas. It was anterior to the inferior vena cava (IVC) and appeared to be compressing the IVC. The mass was suggestive of an abdominal paraganglioma.

Figure 1: CT image showing an abdominal paraganglioma

Other associated endocrine diseases were sort. Since he had a goiter, a ultrasound scan of the thyroid was done, revealing a mild-moderately enlarged gland without nodules or lymphadenopathy. The thyroid functions showed euthyroidism (TSH was 0.4 m iu/mL , Free T4 was 1.36 ng/dl).Fine needle aspiration cytology of the thyroid gland wasThy-2, benign cells. PW had a normal calcium and normal PTH.

Removal of the tumor was planned. Since it was in close proximity and causing compression of the IVC, he was evaluated by the vascular surgical team. Preoperative preparation was initiated to control the heart rate, the blood pressure and the circulatory volume to prevent hemodynamic instability during and after surgery. He was started on phenoxybenzamine 10 mg nocte which was gradually increased to 20 mg twice a day. Postural drop in blood pressure and heart rate was monitored.

PW underwent open laparotomy under the supervision of the most experience Anesthetist available. He was give Intravenous magnesium sulphate (MgSO4) at induction of anesthesia. Mechanism of MgSO4 is by inhibiting catecholamine release, it is also a potential α receptor blocker and useful in controlling catecholamine induced arrhythmias (1). During surgery, endotracheal intubation and direct manipulation of a paraganglioma can precipitate catecholamine release, so continuous cardiac and blood pressure monitoring should be carried out.

During surgery, blood pressure increased which was managed with GTN infusion. Otherwise the surgery was uncomplicated and he recovered without major adverse events. Tumor mass was completely removed and there was no local invasion or spread to regional tissue. Hypotension and hypoglycemia are the most common immediate postoperative complications and should be anticipated (2).

Histology of the resected tumour demonstrated well-defined nests of cuboidal cells with moderately abundant, granular, basophilic cytoplasm separated by highly vascular fibrous septae. Mitotic activity was inconspicuous and the Ki-67 index was <1%. The tumour was completely removed along with the surrounding thin capsule. The cells showed cytoplasmic positivity for neuroendocrine markers; chromogranin, synaptophysin and S100, confirming that it was a paraganglioma.

One to two weeks after surgery urine /plasma fractionated Catecholamines and Metanephrine levels should be carried out, to confirm that the tumour is completely resected. In PW, urinary VMA was used as a marker and it became normal 2 weeks postoperatively.

PW was considered for genetic testing for SDH mutations and he is currently on surveillance for any recurrence. Postoperative surveillance is mandatory to detect metastatic and recurrent disease. According to the 2004 World Health Organization (WHO) criteria, malignant behavior in pheochromocytomas and paragangliomas can only be accurately distinguished by metastatic spread (3). Overall recurrence is high as 15% and is frequently due to appearance of metastasis (4)

Discussion

Pheochromocytomas are rare neuroendocrine tumors arising from chromaffin cells of adrenal medulla. It has an annual incidence of approximately 0.8 per 100,000 (3) and a prevalence that ranges from 0.1-0.6% (2). In an autopsy study, 50% were found to be asymptomatic (6). Paragangliomas are similar extra adrenal tumors that arise from sympathetic and parasympathetic ganglia. Out of chromaffin cell tumours, pheochromocytomas account for 80-85% cases and Paragangliomas account for 15-20%. Epinephrine is secreted exclusively from adrenal glands whereas norepinephrine is secreted from both adrenals and sympathetic ganglia (7).

The biochemical diagnosis of catecholamine excess is established by measuring levels of catecholamines (dopamine, norepinephrine, and epinephrine) or their metabolites (normetanephrine, metanephrines, VMA) in the plasma or urine. Since catecholamines are metabolized inside the tumors to some degree the plasma levels can be falsely low. VMA also lacks sensitivity as it's only positive in about 60% of cases. In addition to that, certain foods and medications can cause false positive elevations.

Superiority of measurement of metanephrines over other tests has been clearly demonstrated (8). Urinary Metanephrine levels by mass spectrometry provide excellent sensitivity (97%) and specificity (91%) (9). Plasma metanephrines also have high sensitivity but is found to be less specific (10).Plasma metanephrines should be done fasting and following 30 min recumbence as when done in seated position false positive level can occur up to 3 folds(11).

After biochemical confirmation of Pheochromocytoma, localizing the site of the tumour is the next step. CT scan with contrast provides an excellent initial method of localization, with a sensitivity between 88 and 100% (12). On CT, Pheochromocytoma will be homogeneous or heterogeneous, necrotic with some calcifications, solid or cystic. Although typically Pheochromocytoma have attenuation values more than 10 HU in non-contrast CT, some cases has been detected with lower attenuation values and contrast washout > 60 % due to high fat content (13).

Surgery in paraganglioma/pheochromocytoma should be well planned. Commencing α- blockers should be done at least 7-14 days prior to surgery (8). Superiority of selective, irreversible and long acting non selective α blockage vs. short acting competitive α-1 blockage is not established. But in a small study done non-selective blockage was associated with better arterial pressure control (14). Nevertheless, it is linked to more postop hypotension. Reflex tachycardia is another adverse side effect of non-selective blockage which is due to lack of noradrenaline re-uptake from the presynaptic membrane with blockage of α 2 receptors.

Once α-adrenergic blockade is established, β-blockers maybe added especially if tachycardia ensues.   β- blockers should never be used alone, as unopposed α-stimulated vasoconstriction may precipitate a hypertensive crisis. The most commonly employed β-blocker is propranolol (β1 and β2 non selective). In PW we used metoprolol (β1 selective), due to presence of congestive cardiac failure.

Other drugs that are employed to control blood pressure and catecholamine excess are calcium channel blockers, tyrosine hydroxylase inhibitor (Metyrosine). Metyrosine inhibits tyrosine hydroxylase, the rate-limiting enzyme of catecholamine biosynthesis which converts tyrosine to DOPA. Metyrosine is generally reserved for patients with a large tumor burden preoperatively and prior to radiofrequency ablation of metastasis where other agents have been ineffective. It is also employed in the long term management of malignant Pheochromocytoma when surgery is contraindicated (15). Most common adverse effect is sedation which is observed in more than 20%. Calcium channel blockers act by inhibiting catecholamine mediated calcium transport in to the vascular smooth muscle triggering vasoconstriction.

In the perioperative period, there is no consensus on the target blood pressure due to lack of randomized control trials. The endocrine society guidelines recommend the blood pressure of less than 130/80 mmHg, with standing systolic pressure greater than 90 mmHg. Heart rate target is 60-80 bpm (8).

Fluid and salt repletion is essential prior to surgery, as they are depleted as a result of excess Catecholamines, which once corrected following surgery, may lead to substantial hypotension.

Most pheochromocytomas are sporadic but nearly 30% is familial. The familial forms includes familial MEN syndromes (MEN IIA and IIB), neuroectodermal disorders like Von-Hippel Lindau syndrome (VHL) and neurofibromatosis type 1 and Succinate Dehydrogenase (SDH) mutations (8). .

Germ line mutations in SDH genes account for most (>80%) of the hereditary paraganglioma/ Pheochromocytoma syndrome (HPGL/PCC)   and <10% of sporadic paragangliomas and pheochromocytomas (16). PW, is planned to have genetic testing for SDH mutations. The probable subtype with the clinical correlation is SDHB as it is the one associated with abdominal, pelvic and mediastinal paraganglioma.

The mean age of tumor presentation in SDHB mutations carriers is around 30 years but, there had been cases that were diagnosed before the age of 10 years suggesting that tumor screening of asymptomatic SDHB carriers should start as early as 10 years of age. SDHB mutations cause malignant HPGL/PCC in 40% or more cases (17).

SDHD mutations are associated with head and neck paragangliomas and occur exclusively when the mutation is transmitted from the father. Others mutations are characterized by autosomal dominant inheritance with variable penetrance. Penetrance by the age of 60 years is>80%.

Succinate Dehydrogenase (SDH) is an enzyme complex located in the inner mitochondrial membrane and contains four subunits encoded by four nuclear genes; SDHA, SDHB, SDHC and SDHD (figure2)
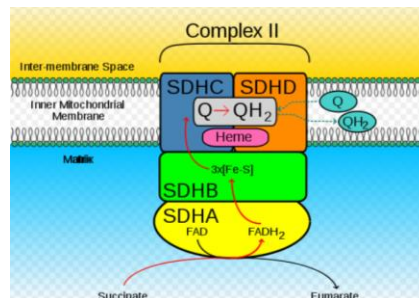

Figure 1: SDHA and SDHB as catalytic subunits, which protrude into the mitochondrial matrix and are anchored

SDH complex leads to oxidation of succinate to fumarate as a part of the Krebs cycle and also causes electron transfer to ubiquinone to prevent formation of potentially dangerous Reactive Oxygen Species (ROS).

Loss-of-function mutations of any of the *SDH* genes or Succinate Dehydrogenase Complex assembly factors (*SDHAF2*) are associated with a variable clinical presentations ranging from early-onset devastating encephalomyopathy, tumour susceptibility in adulthood and optic atrophy in the elderly (18). In addition to HPGL/PCC, SDHX mutations are also associated with gastrointestinal stromal tumours and renal tumors.

The underlying pathogenic mechanism is largely unknown, but it is clear that SDH genes act as classical tumor suppressor genes. Possible mechanisms postulated are the central function in cellular energy production, prevention of ROS formation and prevention of accumulation of succinate which maybe a carcinogenic precipitant.

Accumulation of succinate and the production of reactive oxygen species (ROS) may act independently or in a synergetic manner, leading to hypoxic response despite normoxic conditions (pseudo-hypoxia). In addition to pseudohypoxia, succinate might inhibit apoptosis of neuronal cells or cause dysregulation of the G-protein-coupled receptor (GPCRs). ROS accumulation may result in oxidative damage to DNA.
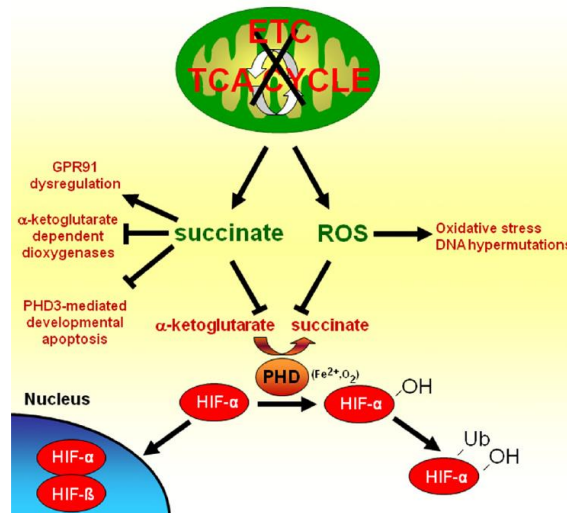

Figure 3: Mechanisms of tumorigenesis due to SDH inactivation mutations

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