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CASE REPORT

EXTREMES OF HYPER AND HYPOTENSIONS IN PHEOCHROMOCYTOMA- A PERIOPERATIVE MANAGEMENT

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ABSTRACT
We report a case of 30 years old female who presented with history of frequent headaches, palpitation, sweating along with mass abdomen. Hypertension was accelerated as ECG reflected sinus rhythm with left ventricular hypertrophy and no papilloedema. Ultrasound abdomen revealed right sided, well defined solid mass posterolateral to the inferior vena cava. Urine analysis revealed raised metabolite vanillylmandalic acid. Patient was diagnosed as a case of pheochromocytoma of the right suprarenal gland. After control of blood pressure, laparotomy under general anaesthesia was performed. A big tumour was excised. Histopathology confirmed the diagnosis of pheochromocytoma.

INTRODUCTION

Pheochromocytoma is a vascular, Catecholamine secreting tumor that consists of cells originating from the embryonic neural crest (chromaffin tissue). Its occurrence rate is rare, exact incidence is not known. It accounts for 0.05 too 0.2% of all cases of hypertension. The tumour is usually benign and located in single adrenal gland in 90% of the cases. Among them 10-15% are malignant, 10-15% bilateral, 10% are extra adrenal known as paragangliomas.[1] The cardinal manifestations of pheochromocytoma are paroxysmal headache, hypertension, sweating and palpitation.[2] Tumours secrete norepinephrine and epinephrine. The diagnosis and management are based on the effects of abnormally high circulating levels of these endogenous adrenergic agonists. Elevated levels of urinary vanillylmandalic acid, norepinephrine and epinephrine provide a highly suggested diagnosis. The location of the tumour is determined by Ultrasonography, scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI).[3]

Before a decision for removal of this tumour is made certain conditions are to be optimized. Preoperatively blood pressure must be controlled. ECG must be without grossly threatening ST-T wave abnormalities. Ideally patient shows no ectopic beats. Orthostatic hypotension above 85/45 mm Hg be observed.[4] Heart rate variations, blood loss and haemostasis are challenging for both anaesthesiologist and surgeon. Handling of tumour during excision cause alarming upsurge in blood pressure which requires infusion of antihypertensive agents and titrating to the desired goals. When tumour is excised one has to take U turn suddenly as the initial desired goals now become problem. The management strategies are to be changed, contrary to the patient's hypertension now hypotension needs aggressive management. Antihypertensive agents are to be substituted with strong vasoconstrictors and inotropes. Swinging between these two extremes of tensions (Hyper and Hypo) a case report describing perioperative management of pheochromocytoma is presented.

CASE REPORT

A 30 years, married, thinly build female patient was admitted with complaints of frequent headache, sweating, sinking of heart sensation and palpitations. She was a known case of hypertension for several months for which she was taking Propranolol 40 mg 8 hourly, prescribed by some general physician. Report of an ultrasound at some civil clinic revealed a space occupying lesion in the liver. Her relevant detailed history including previous surgical history, menstrual, obstetrical history and family history did not depict abnormality. Her pulse at the time of admission was 90/minute. Regular, of no special character. Her Blood Pressure was 230/180 mmHg. Electrocardiogram (ECG) revealed left ventricular hypertrophy. Ultrasound abdomen was repeated, it revealed no focal lesion in the liver, instead a large well defined solid mass measuring 7.6 cm cranio-caudally, 7.2 cm horizontally and 6.5 cm anteroposteriorly (7.6 x 7.2 x 6.5 cm) was seen. Postero-lateral to inferior

vena cava (IVC) pushing it anteriorly and medially, this tumour was also pushing right kidney inferiorly. A thin echogenic rim representing fat was seen separating this tumour from posterior segment of right lobe of liver. There was central area of liquefaction. Para aortic lymph nodes were not seen. There was no ascites. Rest of the abdominal viscera like spleen, kidneys were normal. In complete blood picture patient's Hb was 14.1 Gm/dl. Her erythrocyte sedimentation rate (ESR) was 29 mm fall at the end of first hour, total leukocyte count 10.8 x 10^9/L, neutrophils 75%, (lymphocytes 20%, eoslnophils 03%, and monocytes 02%. Serum urea 8.2 mmol/L, serum sodium 138 mmol/L, serum potassium 4.2 mmol/L, serum glucose (random) 11.4 mmol/L. Urine routine examination was normal. Chest X-ray posteroanterior view showed cardiac enlargement (ECG revealed LVH). The abdomen was not palpated; however inspection did not reveal any abnormality or bulge and hernial orifices were normal. Probable diagnosis of pheochromocytoma of right adrenal gland was made. Urine for vanillylmandalic acid estimation was 115 umol/day. I^{131} metaiodobenzyl guanidine (^{131}I-MIBG) nuclear scan was advised but could not be afforded by the patient. Patient was seen by medical specialist, who omitted propranolol therapy and tablet prazocin (Minipress) 1mg daily was started in addition to tablet Lorazepam (Ativan) 1mg twice daily. Blood pressure (BP) and pulse record was maintained 02 hourly. Salt restriction in diet was advised. After one week patient's BP was in range of 180/140 mmHg (± 10/5 mmHg). Pulse rate was 110 ± 6 beats/min. Patient was collectively managed by anaesthetist, medical specialist and surgical specialist in intensive care unit. Later injection of magnesium sulphate 1 gram I/M 12 hourly and propranolol 40 mg thrice daily were added to the regimen. After another period of 5 days the BP was 150 ± 10mmHg / 105±5 mmHg, pulse rate was 90 ±. 10 beats /min. Haemoglobin was 12.2 g/dl, Hct 37. Two pints of blood were arranged. With all necessary formalities, patient was scheduled for exploratory laparotomy. Patient was shifted to operation theatre as lying case after giving injection midazolam 5 mg and injection Nalbuphine Hcl 5mg intravenously. Size 18 G intravenous (l/V) cannula was aseptically secured on one arm. In OT, Ringer's lactate infusion was started. Additional doses of injection Nalbuphine Hcl 2.5 mg, injection Lignocaine 60 mg and injection magnesium sulphate 1 G I/V were given. Oxygen at the rate of 10 L/min was being administered-with Magil's breathing circuit.

General anaesthesia was induced with injection propofol 4 mg/kg followed by injection Rocuromium 1 mg/kg IV for intubation and additional I/V boluses of 5 mg for maintenance were given. Meanwhile mixture of Isoflurane 2% with 50% nitrous oxide enriched in 50% oxygen was switched on for maintenance of anaesthesia and intermittent positive pressure ventilation at 12 breaths/ min was initiated by Boyle's anaesthesia machine. Lignocaine was sprayed at laryngoscopy and 7 mm internal diameter (ID) cuffed orotracheal tube was quickly and gently placed .It was fixed at length of 21 cm mark at incisors level. In addition to injection Nalbuphine HCL 5mg, injection propranolol 1 mg I/V was given before laryngoscopy & intubation. BP rose to 185/115 mmHg and pulse to 115/ min, in spite of efforts to curtail the haemodynamic stress response to intubation.

A size 18G I/V cannula inserted on other side arm and sodium nitroprusside infusion (Nipride) began and titrated in dose of 5 -10 ug/kg/min. In another burrette 10 mg Glyceryl trinitrate (Isoket) in 100 ml normal saline was prepared and started at rate of 2 ug/kg/min. Monitoring included pulse, BP, O_2 saturation, Electrocardiography, nasopharyngeal temperature, end tidal CO_2, central venous pressure (CVP), pupillary responses, urine output, fluids intake, blood loss measurement. Escort prism (medical data electronics), and normocop Oxy (Datex Engstrom) monitors were used in OT and later on in ITC for above parameters.

An abbocath size 14 catheter was placed in right internal jugular vein and central venous pressure was monitored (5-8 cm of water). A three way connector was affixed to this neckline. While patient was being pre-loaded with I/V fluids containing Ringers Solution and polygeline (1500 ml), two units of her own blood were withdrawn in blood collecting bags. These blood bags were labeled and kept in the same operation room for re-transfusion at the end of operation. Haemoglobin and haematocrit were checked and found to be 10.0 g/dl and 31 respectively. Antibiotic coverage with injection ceftriaxone 1 G I/V 12 hourly, injection amikacin 500 mg I/V 8 hourly, injection metronidazole 500 mg I/V 8 hourly were started before incision. Exploratory laparotomy with roof top incision was performed. An oval tumour measuring 7.6 x 7.2 x 6.5 cm removed after ligating its venous and arterial supply. In fact right adrenalectomy was performed (Fig. 1). Inspite of sodium nitroprusside, GTN infusions and adequate depth of anaesthesia by balanced technique, intermittent injections of 200 ug of propranalol and injection phentolamine (Regitin) in dose of 2.5 mg (boluses) were required. Nevertheless BP recordings revealed mean value of 220 ± 10 / 160 ± 5 mmHg, and mean pulse rate of 136 ± 10/min during surgical manipulation. Once venous drainage of the tumor were ligated BP began to drop to 100/60 mmHg. Retransfusion of

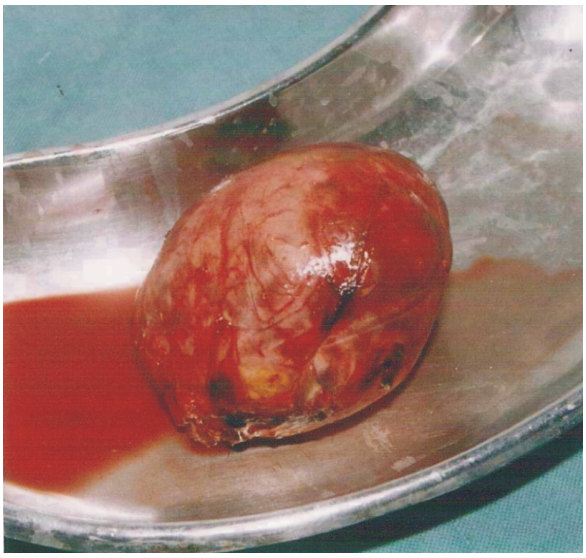

Fig. 1: *A photograph of Pheochromocytoma. The tumour measured 8.5 ×7.6 ×7.2 cm.*

patients own blood was started and I/V crystalloid solution were infused rapidly. Isoflurane inhalation reduced to bear minimum, sodium nitroprusside, GTN infusions, phentolamine and propranolol boluses were omitted. Now 5ug boluses of injection adernaline HCL were repeatedly given. Dopamine HCL 200 mg in 100 ml normal saline at rate of 20ug/ Kg/min and Noradrenatine (Levophed) 8 mg/100 ml at O.lug/kg/min infusions were started to maintain blood pressure at 120 /70 mmHg and pulse rate mean 128 beats/min. Injection Hydrocortisone sodium succinate 200 mg slow I/V boluse was also administered. Abdomen was closed after securing adequate haemostasis and the drains were placed in para-colic gutters. Residual neuromuscular blockade was reversed with injection neostigmine 2.5mg and injection glycopyrolateO.2 mg and patient was extubated on operation table. Haemoglobin and Hct at the end of operation were measured to be 11.8 gm/dl and 36 respectively. Urine output, temperature, SPa02 and end-tidal C02 parameters remained in normal range. Post operative analgesia was provided with injection Nalbuphine HCL 10 mg 8 hourly and Injection Ketorolac (Toradol) 30 mg I/V 12 hourly. Inotropic and steroid supports were tapered off on subsequent days in intensive care Unit. H_2-blocker injection, zantac 50mg i/v 12 hourly for the prevention of stress ulcers was also given. Drains and indwelling urinary catheter removed as per routine hospital protocols. Oral fluids/diet were resumed. Patient was discharged from hospital after removal of stitches. Pulse, BP and urine for VMA (checked after 02 weeks) were in normal limits. Patient was followed up for six months after operation and remained asymptomatic. In recent past the family has shifted to the Province of Sindh.

DISCUSSION

Pheochromocytoma is a vascular tumour of chromaffin tissue, most commonly in the adrenal medulla that produces and secrets epinephrine and norepinephrine[4] 0.05 - 0.2% of hypertensive individuals may have this lesion. While the tumour may be malignant in its behaviour, it is usually benign histologically and located in single adrenal gland in 90% cases. 10-15% are bilateral and also extra adrenal.[21] A retrospective study at Mayo clinic revealed that in 50% of cases the diagnosis was made at autopsy 10% cases were discovered incidentally [5] giving the name 'incidentilomas.

The cardinal manifestations of this tumour are paroxysmal headache, hypertension, sweating and palpitation.[8] The pathophysiology, diagnosis and treatment of these tumours require an understanding of catecholamine metabolism and pharmacology of adrenergic agonists and antagonists. The abnormally high circulating levels of these endogenous adrenergic agonists influence the diagnosis and management of this tumour. Some pheochromocytomas are under neurogenic control.[7] Stress may cause catecholamine levels of 200 - 2000 pg/ml in normal persons. Catecholamine release is stimulated by physiological maneuvers squeezing, palpation of abdomen and handling of tumour; these stimuli may result in blood catecholamine levels of 200, 000 to 1000,000 pg/ml which is a potentially a disastrous situation that should be anticipated and avoided.[8,9] For patients with pheochromocytoma even simple stress can lead to blood catecholamine levels as high as of 2000-20000 pg/ml.

It has been found in several studies that the triad of paroxysmal sweating, hypertension and headache is more sensitive and specific than any laboratory test for diagnosis of pheochromocytoma. These are the symptoms experienced with infusion of epinephrine.[10] Physical examination of the patients is usually unrewarding unless the patient is observed during an attack. Occasionally palpation of the abdomen stimulates the release of catecholamines.

The laboratory measurements of catecholamines or their metabolites have been the standard method of diagnosis. Urinary vanilyl mandalic acid (VMA) estimation of the patient was 115 umol/day (normal range for adults is 7 - 33 umol/day). Triad of hypertension, headache and sweating are usually indications for these metabolites estimation in urine. In more than 85% of cases these are sporadic tumours of unknown cause that are localized in the medulla of one adrenal gland. However these

vascular tumours can occur anywhere in body and can be found in right atrium, the spleen, the broad of the ovary, the organ of Zukerkandl at the bifurcation of aorta. Occasionally this tumour is familial with autosornal dominant trait. It may be a part of polyglandular neoplastic syndrome known as multiple endocrine adenoma type I a or type llb. Often bilateral tumours are present in the familial form.[11] Specific mutations of the PET proto-oncogene cause familial pre-disposition to pheochromocytoma. Recent findings demonstrating extra ordinary high sensitivity of plasma levels of metanephrines for detecting this tumour have led to an algorithm for diagnosis. Nuclear imaging approach such as 1^{131} metaiodobenzyl guanidine (^{131}I-MIBG) scintigraphy and 6 - [(16) F] fluorodopamine positron emission tomography enhance both diagnosis and localization of the tumour. Areas requiring further work include determining appropriate follow up of patients with familial pheochromocytoma, elucidating the bases for phenotype differences, improving specificity and sensitivity of biochemical tests in addition to testing the risk for tumour recurrence, after partial adrenalectomy. ^{131}I - MIBG scintigraphy is advised especially If malignant nature of pheochromocytoma is suspected or established. This is done before and after high dose MIBG treatment based on protocols of Rose et al.[12]

Preoperative assessment should focus on the adequacy of adrenergic blockade and volume replacement. Specifically resting, orthostatic blood pressure, heart rate changes, ventricular ectopy and electrocardiographic evidence of ischaemia should be evaluated. A decrease in plasma volume and red cell mass contributes to the severe chronic hypovolaemia seen in these patients. Although the haematocrit is usually elevated or normal, it does not reflect the volume status. Pre-operative alpha-adrenergic blockade with phenoxybenzamine helps correct the volume deficit in addition to correcting hypertension and hyperglycaemia.

A drop in haematocrit should accompany the expansion of circulatory volume. This often unmasks an underlying anaemia. Potentially life threatening variations in blood pressure particularly during induction and manipulation of the tumour indicate the need for direct arterial pressure monitoring. Large intraoperative fluid/ volume shifts underscore the importance of good intravenous access and urinary output monitoring. young patients with healthy hearts probably only need central venous pressure monitoring although patients with evidence of catecholamine induced cardiomyopathy may benefit from the use of a pulmonary artery catheter.[13] The elevated systemic vascular resistance index (SVRI) with low cardiac index (Cl) was considered to result from increased alpha – adrenergic activity secondary to Beta -adrenergic block. Clinicians should be aware of the possibility of hypertensive crisis after labetalol.[14]

To avoid or lessen the chances of stress response a deep level of anaesthesia is to be established, till that time laryngoscopy and intubation should not be attempted. For control of intraoperative hypertension sodium nitroprusside, glyceryl trinitrate, phentolamine or nicardipine can be used,[14] Nitroprusside was found more effective due to rapid onest of action and titrable dosage in addition to short duration of action. In our patient we used infusion of sodium nitroprusside, GTN infusion, boluses of phentolamine and propranalol to control rises in blood pressure. In order to prevent sympathetic stimulation we also avoided hypoventilation. We used injection Rocuronium for muscle relaxation and drugs like pancuronium were not used due to their action to inhibit parasympathetic nervous system. Propofol at the rate of 8 ml/hour i/v were used intraoperatively in infusion in form supplementing O_2 40% and N_2O 60% concentration. As expected, after ligation and removal of the tumour, hypotension was of main concern for which fluid resuscitation included i/v polygeline/ gelatin (Haemaccel) and retransfusion of patients own blood (O_2 units) which was withdrawn after induction of general anaesthesia. Hypotensive drugs were replaced with i/v infusion of noerpinephrine (levophed) 8mg/100ml and titrated in the range of .05 – 1.0ug/kg/min. 5 ug boluses of injection adrenaline HCl were also used intermittently. Propofol infusion was reduced to 4 ml/min; urine out put remained in the range of 1 - 1.5 ml/min, intraoperatively CVP ranged between 5 - 8 cm H_2O. Nasopharyngeal temperature remained in normal range (35.5 - 37°C). Post operatively injection Nalbuphine 10mg 8 hourly, injection Ketorolac (Toradol) 30 mg I/V 12 hourly were used for analgesia. Sedation with injection midazolam 1 mg I/V 2 hourly was also supplemented. Patient made an uneventful recovery and was discharged after removal of stitches on 10th post operative day. Post operatively if hypertension occurs, it may be due to volume overload, pain, anxiety or any remnant occult tumour.[15] Patient was followed up for six months after operation and was found asymptomatic.

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