

EXTREMES OF ... TENSIONS IN PHEOCHROMOCYTOMA (A PERIOPERATIVE MANAGEMENT)

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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 pheochromo-cytoma of the right suprarenal gland. After control of blood pressure, laparotomy under general anesthesia was performed. A huge tumor was excised. Histopathology confirmed pheochromocytoma.

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 0.2 - 2.0% of all cases of hypertension. The tumor is usually benign and located in single adrenal gland in 90% of the case. 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 Tumors 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 tumor is determined by Ultrasonography, scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI).³

Before a decision for removal of this tumor is made certain conditions are to be optimized. Pre-operatively blood pressure must be controlled. ECG must be without grossly threatening ST-T wave abnormalities. Ideally patient be without ectopic beats. Orthostatic hypotension above 85/45 mm Hg be observed.⁴ Heart rate variations, blood loss and hemostasis are challenging for both anesthesiologist and surgeon. Handling of tumor during excision cause alarming upsurge in blood pressure which require infusion of antihypertensive agents and titrating to desired

goals. When tumor 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 known case of hypertension for several months for which she was taking tab Propranolol 40 mg 8 hourly, prescribed by some general physician. Report of an ultrasound done 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 tumor was also pushing right kidney inferiorly. A thin echogenic rim representing fat was seen separating this tumor 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 was normal. In blood complete picture report 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 $10.8 \times 10^9/L$, neutrophils 75%, (lymphocytes 20%, eosinophils 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 right adrenal gland was made. Urine for vanillylmandelic acid estimation was 115 $\mu\text{mol/day}$. ^{131}I -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 prazosin (Minipress) 1mg daily was started in addition to tablet Lorazepam (Ativan) 1mg twice daily. 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 ($\pm 10/5$ mmHg). Pulse rate was 110 ± 6 beats/min. Patient was collectively managed by Anesthetist, Medical Specialist and Surgical Specialist in intensive care unit. Later injection Magnesium sulphate 1 gram I/M 12 hourly and tab propranolol 40 mg thrice daily were added to the regimen. After another period of 5 days the BP was 150 ± 10 mmHg / 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 (I/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 @10 L/min was being administered-with Magil's breathing circuit.

General Anesthesia was induced with injection propofol 4 mg/kg followed with injection

Rocuroium 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 anesthesia and intermittent positive pressure ventilation at 12 breaths/min was initiated by Boyle's anesthesia 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 hemodynamic 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 $\mu\text{g/kg/min}$. In another burette 10 mg Glyceryl trinitrate (Isoket) in 100 ml normal saline was prepared and started at rate of 2 $\mu\text{g/kg/min}$. 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 abocath 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. Hemoglobin 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 tumor measuring 7.6 x 7.2 x 6.5 cm removed after ligating its venous and arterial supply. In fact right adrenalectomy was performed (Photograph). In spite of sodium nitroprusside, GTN infusions and adequate depth of anesthesia by balanced technique, intermittent injections of 200 μg of propranolol and Injection phentolamine (Regitin) in dose of 2.5 mg (boluses) were required. Nevertheless BP recordings revealed

mean value of $220 \pm 10 / 160 \pm 5$ 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 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 Adrenaline HCL were repeatedly given. Dopamine HCL 200 mg in 100 ml Normal Saline at rate of 20ug/Kg/min and Noradrenaline (Levophed) 8 mg/100 ml at 0.1ug/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 glycopyrolate 0.2 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, SpO₂ and end-tidal CO₂ 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. 1-12 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 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 Sindh Province.

DISCUSSION

Pheochromocytoma is a vascular tumor of chromaffin tissue, most commonly in the adrenal medulla that produces and secretes epinephrine and norepinephrine⁴ 0.05 - 0.2% of hypertensive individuals may have this lesion. While the tumor may be malignant in its behavior, It is usually benign histologically and located in single adrenal gland in 90% cases. 10-15% is bilateral and also extra adrenal.²¹ A retrospective study at Mayo clinic revealed that in 50% of case the diagnosis was made at autopsy 10% of cases were discovered incidentally [5] giving the name 'incidentalomas'.

The cardinal manifestations of this tumor are

paroxysmal headache, hypertension, sweating and palpitation.⁸ The pathophysiology, diagnosis and treatment of these tumors 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 tumor. 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 tumor; these stimuli may result in blood catecholamine levels of 200, 000 to 1000,000 pg/ml which is a potentially 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.

However the laboratory measurements of catecholamines or their metabolites have been the standard method of diagnosis. Urinary vanillyl 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 is usually an indication for these metabolites estimation in urine In more than 85 % of cases these are sporadic tumors of unknown cause that are localized in the medulla of one adrenal gland. However these vascular tumors can occur anywhere in body but commonly are found In right atrium, the spleen, the broad ligament of the ovary, the organ of Zuerkandl at the bifurcation of aorta. Occasionally this tumor is familial with autosomal dominant trait. It may be a part of polyglandular neoplastic syndrome known as multiple endocrine adenoma type I a or type IIb. Often bilateral tumors 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 tumor have led to an algorithm for diagnosis. Nuclear Imaging approach such as ¹³¹I metaiodobenzyl guanidine (¹³¹I-MIBG)

scintigraphy and 6 - [(16) F] fluorodopamine positron emission tomography enhance both diagnosis and localization of the tumor. 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 tumor recurrence, after patient adrenalectomy. ¹³¹I - 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 (2003).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 hypovolemia seen in these patients. Although the hematocrit 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 hyperglycemia.

A drop in hematocrit should accompany the expansion of circulatory volume. This often unmasks an underlying anemia. Potentially life threatening variations in blood pressure particularly during induction and manipulation of the tumor 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 (CI) 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 onset 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 propranolol 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 rate of 8 ml/hour I/V were used intraoperatively in infusion from supplementing O₂ 40% and N₂O 60% concentration. As expected, after ligation and removal of the tumor, hypotension was of main concern for which fluid resuscitation Included I/V polygeline/ gelatin (Haemaccel) and retransfusion of patients own blood (O₂ 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 ug/min; urine out put remained in the range of 1 - 1.5 ml/min, intraoperatively CVP ranged between 5 - 8 cm H₂O. Nasopharyngeal temperature remained in normal range (35.5 - 37°C). Post operatively injection Nalbuphine 1mg 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 occur, it may be due to volume overload, pain, anxiety or any remnant occult tumor.¹⁵ Patient was followed up for six months after operation and was found asymptomatic.

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