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An Unusual Presentation Of Pheochromocytoma Induced Cardiomyopathy

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Abstract

Pheochromocytoma is a rare neuroendocrine tumor located in the suprarenal or adrenal glands leading to increased production and release of catecholamine and multiorgan involvement sequelae. Pheochromocytomas are mostly benign in nature that arise from the chromaffin cells within the adrenal medulla or anywhere in the sympathetic nerve plexus also called paragangliomas or extra-adrenal pheochromocytomas. The incidence of Pheochromocytoma and Paragangliomas ranges from 0.04 to 0.95 cases per 100000 per year. Typical symptomatology include headache, palpitations, sweating, intermittent or persistent hypertension, abdominal pain, shock, ARDS, pulmonary edema, anxiety, hyperthermia, tachyarrhythmias and less frequently cardiogenic shock. Catecholamine induced cardiomyopathy in Pheochromocytoma is a comparatively rare but very difficult to treat complication of pheochromoctyoma. Therefore, these rare cardiovascular manifestations as the first symptoms of pheochromocytoma often lead to a delay in diagnosis. Herein, we a report a case of patient with Pheochromocytoma induced cardiomyopathy which produced a diagnostic dilemma on the clinical presentation. In addition the patient had hypotension. It was successfully treated with surgical excision after medical stabilisation.

Keywords: Pheochromocytoma, cardiomyopathy, catecholamine, adrenal

Introduction

Pheochromocytoma is a rare neuroendocrine tumor located in the suprarenal or adrenal glands leading to increased production and release of catecholamine and multiorgan involvement sequelae.[1] Pheochromocytomas are mostly benign in nature that arise from the chromaffin cells within the adrenal medulla or anywhere in the sympathetic nerve plexus also called paragangliomas or extra-adrenal pheochromocytomas.[2] The incidence of Pheochromocytoma and Paragangliomas ranges from 0.04 to 0.95 cases per 100000 per year.[3] These tumors can occur sporadically or due to germline mutations of several tumor susceptibility genes like REarranged during Transfection (RET) proto-oncogene, von Hippel-Lindau disease tumor suppressor gene *(*VHL*)*, neurofibromatosis type 1 tumor suppressor gene *(*NF 1*)*, genes encoding four succinate dehydrogenase complex (SDH) subunits (SDHx*; i.e.* SDHA, SDHB, SDHC, and SDHD genes), gene encoding the enzyme responsible for flavination of the SDHA subunit (SDHAF2 or SDH5 gene) and newly described tumor suppressor TMEM127 gene.[4] Germline mutations is to be found in 100% of syndromic cases and in about 90% of patients with positive familial history and in non-syndromic patients with apparently sporadic tumors the frequency of genetic mutations has been recorded up to 27%.[4] Typical symptomatology

include headache, palpitations, sweating, intermittent or persistent hypertension, abdominal pain, shock, ARDS, pulmonary edema, anxiety, hyperthermia, tachyarrhythmias and less frequently cardiogenic shock.[5,6] Severe cardiovascular complications are associated with hypertensive crisis due to excessive catecholamine release.[7] Acute or chronic hypertension can lead to myocardial ischemia leading to acute (ischemic or Takotsubo) or chronic (hypertrophic or dilated) cardiomyopathy.[8-10] Catecholamine induced cardiomyopathy in Pheochromocytoma is a comparatively rare but very difficult to treat complication of pheochromoctyoma.[7] It has been proposed that chronic or acute catecholamine intoxication may lead to these structural myocardial alterations.[11-13] Therefore, these rare cardiovascular manifestations as the first symptoms of pheochromocytoma often lead to a delay in diagnosis. Herein, we a report a case of patient with Pheochromocytoma induced cardiomyopathy which produced a diagnostic dilemma on the clinical presentation. In addition the patient had hypotension. It was successfully treated with surgical excision after medical stabilisation.

Case Capsule

A 51-year old woman without prior medical history came to the Emergency Room with continuous dull aching epigastric pain, chest stuffiness, generalised weakness, multiple episodes of non-bilious and non-projectile vomiting and NYHA grade 3 dyspnea. All these symptoms except dyspnea had been ongoing for 5 days and the patient was treated with antibiotics, antispasmodics and antacids at a local hospital before admission. Patient was a known Diabetic well controlled on oral Anti-Diabetic drugs. She disclaimed any surgical history or any family history of Kochs, Kochs contact, pulmonary or cardiovascular diseases.

At time of presentation, the patient was confused and the physical examination revealed a blood pressure of 80/60 mmHg, pulse rate of 138 beats per minute, saturation of 70% on room air, and a respiratory rate of 24 breaths per minute. Chest auscultation revealed normal S1 and S2 heart sounds with diffuse moist bilateral rales in the lungs. An abdominal examination revealed epigastric tenderness. Remaining examination findings were unremarkable. After appropriate resuscitative measures comprising of aggressive fluid therapy and oxygen support patient was shifted to the ICU. Laboratory investigations revealed an ABG showing metabolic acidosis Ph- 7.30, bicarbonate- 17.3 mmol/L, PCO2- 20.8 mmHg. Other investigations showed TLC- 15,430; Hb- 11.2; HGT- 176 mg/dl; SGOT/SGPT- 71/89; Na- 132; raised CPK-MB of 43 U/L (reference range- 7 to 25); raised NT-PRO BNP 22334 pg/ml (reference range 0-125); and elevated TROPONIN T levels of 0.149 ng/ml (reference range- 0.00 to 0.1). Rest of the laboratory parameters were unremarkable. ECG showed sinus tachycardia and ischaemic changes (ST segment depression in II, III, AVF, V3 and V4). Patient was reviewed by Cardiologist and she was subjected to Echocardiogram that revealed- Dilated Cardiomyopathy, dilated LA and LV, global LV hypokinesia, LVEF- 20%, mild AR and TR with dilated IVC. Chest X ray showed bilateral pleural effusion with pulmonary edema.

Patient had persistent hypotensive episodes and therefore was started on Nor-adrenaline support. Once medically stabilised she was subjected to CT scan of Chest and Abdomen + Pelvis that revealed moderate pleural effusion and pulmonary oedema and in CT Abdomen + Pelvis showed (Figures 3,4,5) Hepatomegaly, a well-defined heterogeneously enhancing soft tissue lesion in the left suprarenal location measuring 5.6cm x 5.4cm x 5.7cm abutting and compressing the superior aspect of the left kidney with irregular hypodense to non-enhancing areas within the lesion suggestive of necrotic areas. Considering all the symptoms and the chest and abdomen CT results, the diagnosis was suspected to be acute heart failure, pheochromocytoma induced cardiomyopathy. Immediate endocrinologist opinion was taken and she was started on rate control drugs with anti-hypertensives thus targeted BP in the range of 90 systolic with heart rate below 100 beats per minute. Continued non-invasive ventilation, torsemide, digoxin were administered to correct heart failure. Plasma metanephrines-free was raised 126 pg/ml (reference range- <100); elevated Dopamine level 190 pg/ml (reference range- <100); raised morning (7-9am) Cortisol level 228.9 mcg/dl (reference range- 4.3 to 22); Rest Nor-Metanephrine-Free Plasma, ACTH, and Renin levels were within normal limits. Gallium-68 DOTATOC scan (Figures 1 and 2) revealed High grade uptake (SUV max 38.8) somatostatin receptor activity in the lesion in the left

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suprarenal gland measuring 5.5cm x 5.3cm x 5.0cm with internal areas of necrosis raising possibility of Pheochromocytoma with normal contralateral adrenal gland. Patient was planned for Open Left Adrenalectomy. The patient was reviewed by the endocrinologist for adequate preoperative preparation, which included BP control with phenoxybenzamine and metoprolol and an injection of normal saline for preventing severe hypotension after tumor resection. After appropriate resuscitative measures, stabilisation, BP control and after consenting, patient was shifted to the Operation Room. Left adrenalectomy by open approach was successfully performed (Figures 6 and 7). Histopathological section revealed a well circumscribed neoplasm composed of neoplastic cells arranged in zell-ballen pattern and trabecular pattern. Individually the neoplastic cells are large, polygonal with granular cytoplasm. Nuclei is oval and uniform with prominent nucleoli. No capsular and vascular, adrenal adipose invasion seen without mitotic activity. The lesion is surrounded by compressed rim of adrenal cortex and fibrotic tissue (Figure 8).

Her vitals and laboratory parameters normalised 2 days after surgery. 8 days after surgery, she was discharged in good condition. During 3 months of regular follow-up, she had no dyspnea, weakness, headache, emesis or pain in abdomen. Her cardiac markers, plasma metanephrine, cortisol were within the normal range. The findings of 24- hour ambulatory BP monitoring, ECG, Echocardiography (LVEF- 55%, no evidence of Cardiomyopathy) were normal. Adrenal CT scan did not reveal any new lesions. She was advised to follow-up on a regular basis.

Discussion

Pheochromocytoma is a neuroendocrine tumor causing classical triad of headache, palpitations and paroxysmal hypertension with sweating.[14] As a result of different forms and amounts of secretion of catecholamines, the clinical features are difficult to identify. Some patients are even asymptomatic.

Pheochromocytoma is a great disease imitator.[7] Recognition requires a high degree of suspicion as it may present atypically including acute and chronic cardiac myopathies, pulmonary oedema, cardiogenic shock and sudden death.[7] It is relatively an uncommon diagnosis. McNeil et al showed a retrospective study of 38,596 autopsies from Australia that the tumor is being present in up to 1:2000 autopsies.[15] Mayo clinic retrospective study, from the years of 1950 through 1979, showed that 11 cases of pheochromocytoma were diagnosed in an average of population of around 45,800.[16] Swedish cancer registry found out that 42% of pheochromocytoma were first diagnosed after death.[17]

This patient with pheochromocytoma tumor started with a crisis of dilated cardiomyopathy induced by catecholamines, with a picture of acute heart failure and abdominal symptoms secondary to acute tumor necrosis. This is an unusual presentation that is difficult to diagnose. Cardiomyopathy in pheochromocytoma is produced by raised catecholamine levels, with an overload of intracellular calcium, an ischemia-reperfusion type of lesion with generation of free radicals, and degradation of myocardial fibers.[18] The patient can present with clinical signs of acute heart failure with dilated cardiomyopathy or non-cardiogenic pulmonary oedema, fatal arrythmia and sudden death.[19] Catecholamines can cause tachycardia-induced cardiomyopathy or aggravate a pre-existing cardiac condition. Excessive adrenergic stimulation may cause coronary vasoconstriction and vasospasm, resulting in ischemia of myocardium and cardiomyopathy.[20]

During physiologic conditions, secretion of catecholamine is controlled and regulated. In pheochromocytoma, catecholamines are often secreted in an uncontrollable manner.[21] Other mechanisms involved in catecholamine induced cardiomyopathy include beta-1 adrenoreceptors desensitization, intracellular calcium overload, increased oxidative stress, mitochondrial dysfunction and ischemia. The excessive excitation of beta-1 adrenoreceptors increases the inotropic and chronotropic activities of the heart that increases the myocardial oxygen demand, reducing oxygen delivery and producing hypoxic areas in the heart.[22,23] Increased accumulation of calcium in the mitochondria initiates oxidative stress and mitochondrial permeability transition leading to cell death and necrosis.[23] The oxidation of catecholamines also produces cardiotoxicity.[24]

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Catecholamines also exert a receptor mediated effect on the myocardial cell. Long term rise in catecholamine levels leads to downregulation of beta-adrenergic receptors, inducing suboptimal myocardial functioning as well as decreased number of myocardial contracting units.[25] Oxidized catecholamines can also increase the permeability of sarcolemmal membrame, leading to influx of calcium ions and thus the sequelae.[26] This results in acute myocarditis and myocardial necrosis as well as reduced cardiac output culminating in cardiogenic shock as seen in this patient.

Prompt diagnosis remains difficult in these patients with such atypical presentations. In this case, the patient's history of abdominal pain and presentation led to an early CT scan of abdomen and the diagnosis of adrenal mass was made. Elevated catecholamines, metanephrines, cortisol reinforced the diagnosis of pheochromocytoma. Treatment involves hemodynamic stabilization of the patient with aggressive fluid resuscitation as first line therapy, vasopressors and inotropic support if needed. This is followed by medical treatment with an alpha-blocker and beta-blocker to control the blood pressure and heart rate.

Pheochromocytoma with atypical symptomatology remains undiagnosed in many patients despite adequate investigations, leading to lethal complications and outcome. Therefore, it is essential to raise a high index of suspicion to achieve early diagnosis in patients with atypical presentations such as acute heart failure and cardiomyopathy to improve the patient outcome.

Conclusion

Pheochromocytoma and Paraganglioma is a great disease imitator, and remains undiagnosed in many patients presented with atypical symptoms. It may present atypically as acute or chronic cardiomyopathies, pulmonary oedema, severe sepsis, myocarditis, acute myocardial infarction and cardiogenic shock.

We report an unusual presentation of pheochromocytoma without hypertension complicated by acute heart failure and cardiomyopathy. Early diagnosis is essential to initiate appropriate therapeutic measure and reverse cardiomyopathy at an early stage. The key to successful treatment of Catecholamine induced is an early recognition of different clinical signs and symptoms directed to the detection of pheochromocytoma, adopting appropriate diagnostic procedures, administration of appropriate medical therapy and definitive surgery once medical stabilization is achieved.

Moreover, a differential diagnosis of pheochromocytoma induced cardiomyopathy should be considered for patients presenting with uncommon heart failure, in hypotensive patients.

References

1. R. W. Gifford Jr., E. L. Bravo, and W. M. Manger, "Diagnosis and management of pheochromocytoma," Cardiology, vol. 72, no. 1, pp. 126–130, 1985.
2. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005;366:665–75.
3. Al Subhi AR, Boyle V, Elston MS. Systematic Review: Incidence of Pheochromocytoma and Paraganglioma Over 70 Years. J Endocr Soc. 2022 Jul 3;6(9):bvac105. doi: 10.1210/jendso/bvac105. PMID: 35919261; PMCID: PMC9334688.
4. Karasek D, Frysak Z, Pacak K. Genetic testing for pheochromocytoma. Curr Hypertens Rep. 2010 Dec;12(6):456-64. doi: 10.1007/s11906-010-0151-1. PMID: 20938758; PMCID: PMC3061287.
5. C. C. Solorzano, J. Parks, and R. A. Prinz, "Pheochromocytoma presenting with multiple organ failure," American Surgeon, vol. 74, no. 11, pp. 1119–1121, 2008.
6. W. Peter, B. G. Jacob, D. Engelhardt, and W. Decker, "An usual cause of acute lung edema requiring artificial respiration in a 25-year-old patient. Adrenal pheochromocytoma," Der Internist, vol. 43, no. 10, pp. 1285–1288, 2002.
7. Steppan J, Shields J, Lebron R. Pheochromocytoma presenting as acute heart failure leading to cardiogenic shock and multiorgan failure. Case Reports in Medicine. 2011 Jan 1;2011.
8. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: Characteristics and treatment. Endocrinol Metab Clin North Am 2011; 40: 295–311.

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9. Kalra Y, Agarwal H, Smith A. Perioperative management of pheochromocytoma and catecholamine-induced dilated cardiomyopathy in a pediatric patient. Pediatr Cardiol 2013; 34: 2013–3016.
10. Kobayashi Y, Kobayashi Y. Pheochromocytoma Found in Takotsubo Cardiomyopathy Patients. J Invasive Cardiol 2014; 26: E76–E77.
11. Coupez E, Eschalier R, Pereira B, et al. A single pathophysiological pathway in Takotsubo cardiomyopathy: catecholaminergic stress. Arch Cardiovasc Dis. 2014;107:245–252.
12. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352:539–548.
13. Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine mediated myocardial stunning? Cell Mol Neurobiol. 2012;32:847– 857.
14. Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon JS, Heaney AP, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. Pancreas. 2017;46(6):707–14.
15. A. R. McNeil, B. H. Blok, T. D. Koelmeyer, M. P. Burke, and J. M. Hilton, "Phaeochromocytomas discovered during coronial autopsies in Sydney, Melbourne and Auckland," Australian and New Zealand Journal of Medicine, vol. 30, no. 6, pp. 648– 652, 2000.
16. B. M. Beard, S. G. Sheps, L. T. Kurland, J. A. Carney, and J. T. Lie, "Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979," Mayo Clinic Proceedings, vol. 58, no. 12, pp. 802–804, 1983.
17. G. Stenstrom and K. Svardsudd, "Pheochromocytoma in Sweden 1958–1981. An analysis of the National Cancer Registry Data," Acta Medica Scandinavica, vol. 220, no. 3, pp. 225–232, 1986.
18. De Souza F, Altenburg R, Henriques Cunha Neto S, de Mattos MA. Tako-tsubo-like cardiomyopathy and extra-adrenal pheochromocytoma: case report and literature review. Clin Res Cardiol. 2008;97:397–401.
19. Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of phaeochromocytoma. J Hypertens. 2011;29:2049–60.
20. Scott, R. Parkes, and D. P. Cameron, "Phaeochromocytoma and cardiomyopathy," Medical Journal of Australia, vol. 148, no. 2, pp. 94–96, 1988.
21. Chen Y, Best JA, Nagamoto K, Tan AW. Regulation of tyrosine hydroxylase gene expression by the m1 muscarinic acetycholine receptor in rat pheochromocytoma cells. Brain Res Mol Brain Res 1996; 40: 42–54.
22. Costa VM, Carvalho F, Bastos ML, Carvalho RA, Carvalho M, Remiao F. Contribution of catecholamine reactive intermediates and oxidative stress to the pathologic features of heart diseases. Curr Med Chem 2011; 18: 2272–2314.
23. Khan MU, Cheema Y, Shahbaz AU, Ahokas RA, Sun Y, Gerling IC, Bhattacharya SK, Weber KT. Mitochondria play a central role in nonischemic cardiomyocyte necrosis: Common to acute and chronic stressor states. Pflugers Arch 2012; 464: 123–131.
24. Behonick GS, Novak MJ, Nealley EW, Baskin SI. Toxicology update: the cardiotoxicity of the oxidative stress metabolites of catecholamines (aminochromes). J Appl Toxicol 2001; 21: (Suppl 1): S15–S22.
25. T. A. Kassim, D. D. Clarke, V. Q. Mai, P. W. Clyde, and K. M. Mohamed Shakir, "Catecholamine-induced cardiomyopathy," Endocrine Practice, vol. 14, no. 9, pp. 1137–1149, 2008.
26. B. Schifferdecker, D. Kodali, E. Hausner, and J. Aragam, "Adrenergic shock—an overlooked clinical entity?" Cardiology in Review, vol. 13, no. 2, pp. 69–72, 2005.

Figures

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FIGURE 1- Gallium-68 DOTATOC scan showing a well-defined homogenously enhancing soft tissue density with internal necrotic areas in the left suprarenal region measuring 5.5cm x 5.3cm x 5cm

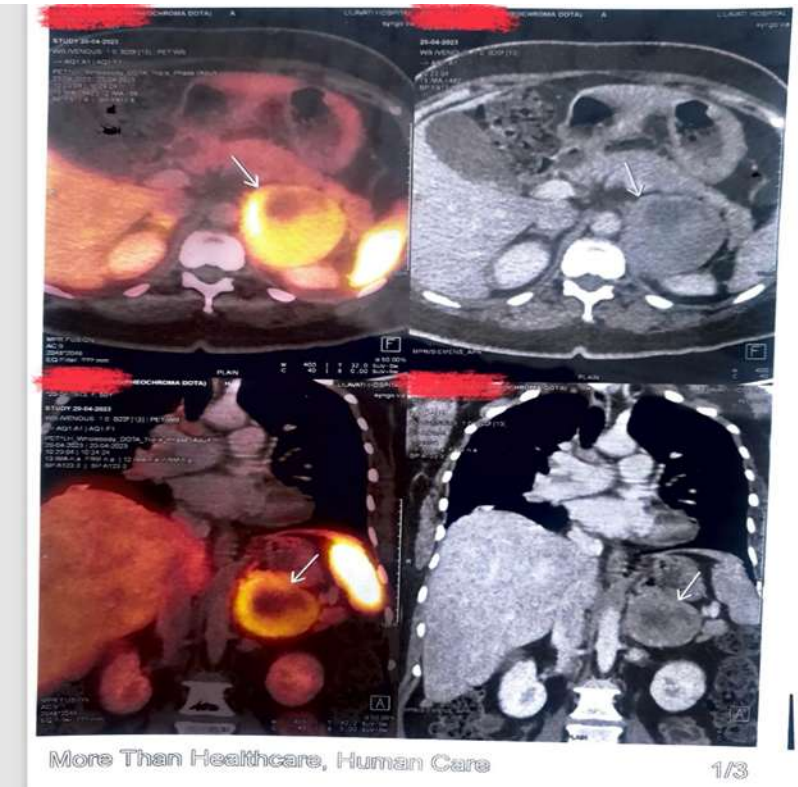

FIGURE 2- Gallium-68 DOTATOC scan showing left adrenal mass

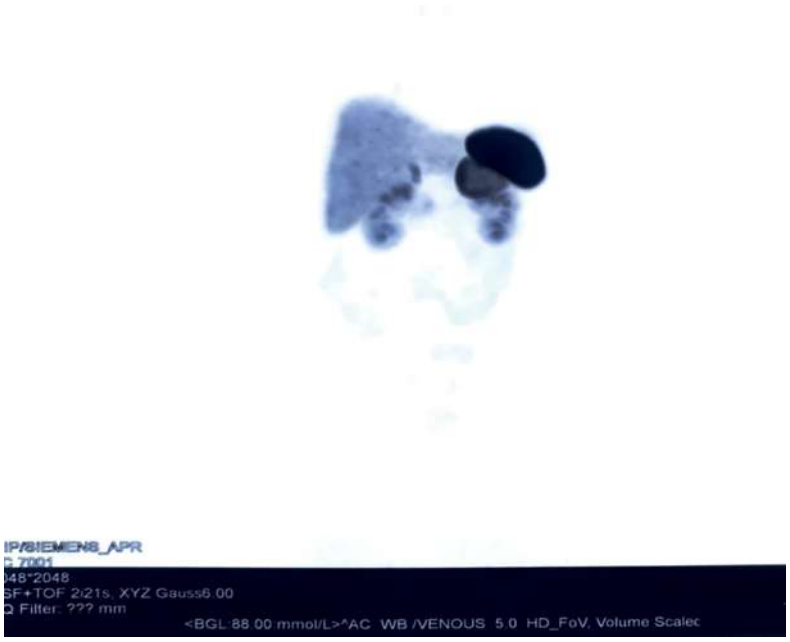

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FIGURE 3- CT Abdomen and Pelvis Axial view showing a well-defined, heterogeneously enhancing soft tissue lesion of size measuring 5.6cm x 5.4cm x 5.7cm is the left suprarenal region abutting the left kidney with hypodense necrotic areas within this lesion

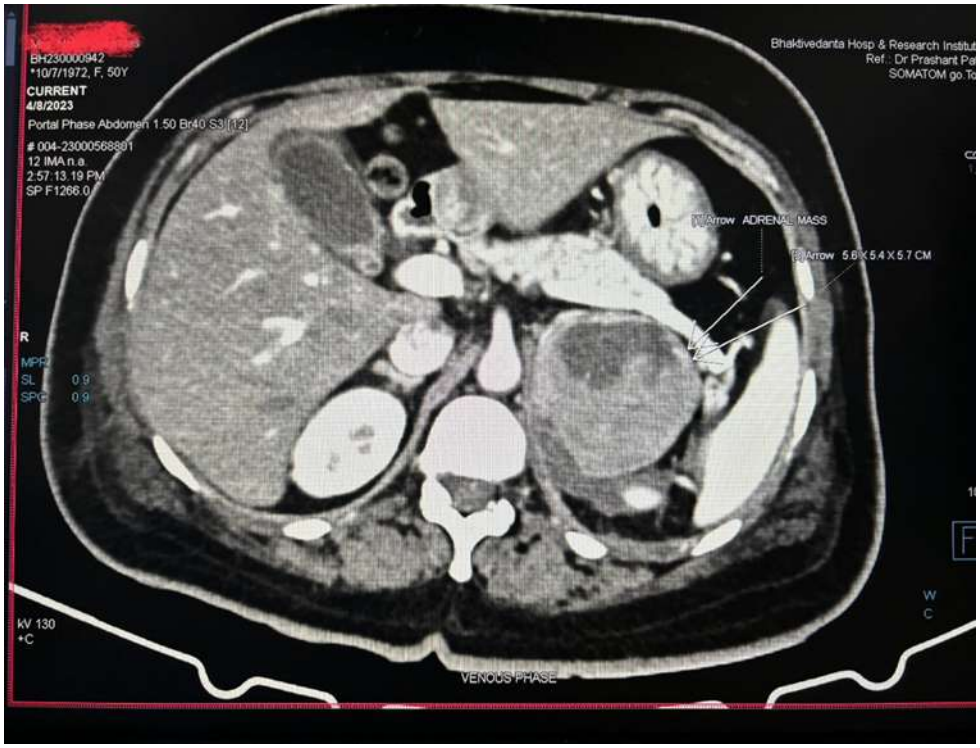

FIGURE 4- CT Abdomen and Pelvis Coronal view showing left adrenal mass

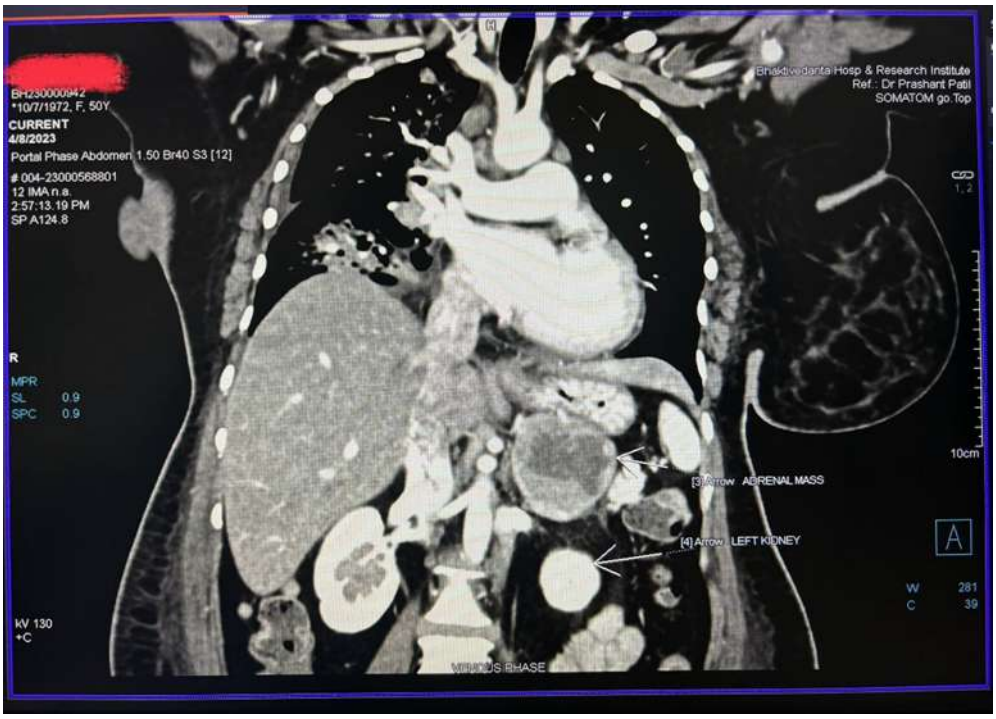

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FIGURE 5- CT Abdomen and Pelvis Sagittal view showing left adrenal mass

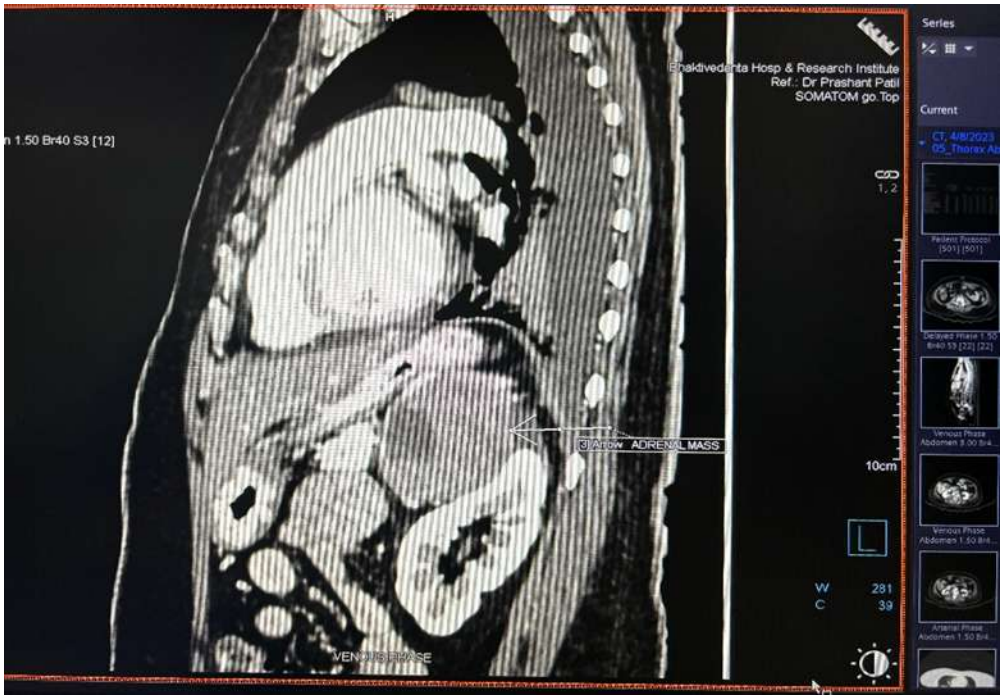

FIGURE 6- Intraoperative image of left open adrenal adrenalectomy through Left flank (11th rib) incision

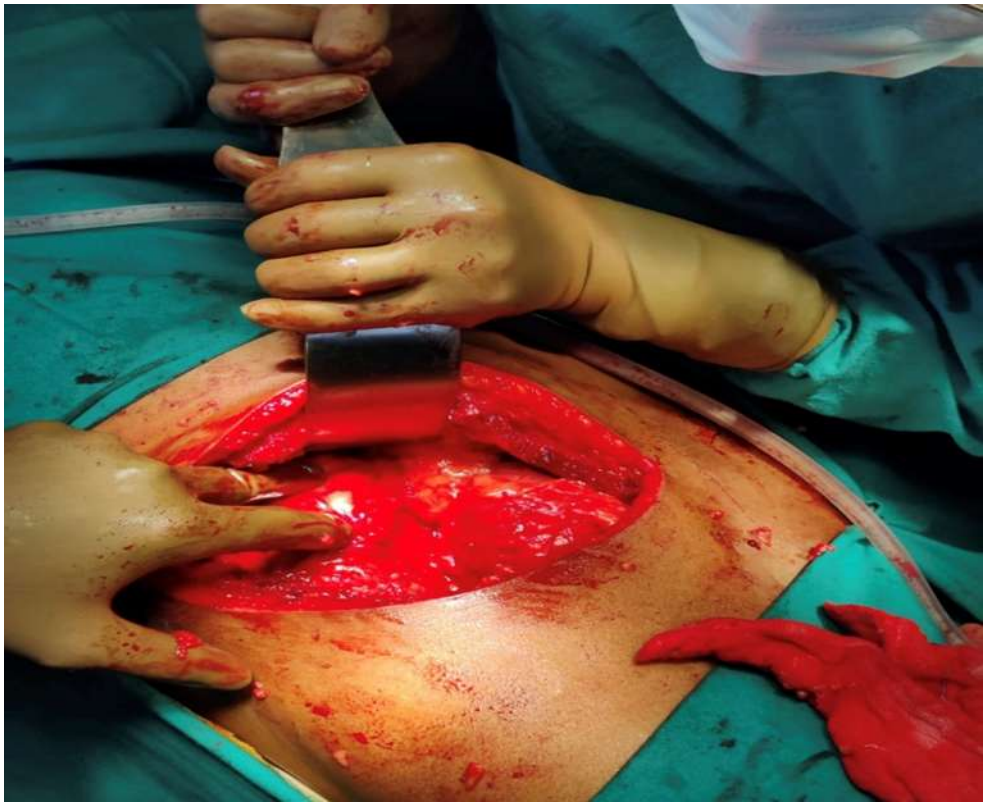

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FIGURE 7- Excised specimen of left adrenal mass, well-defined round to ovoid, vascular, measuring 5.9cm x 5.7cm

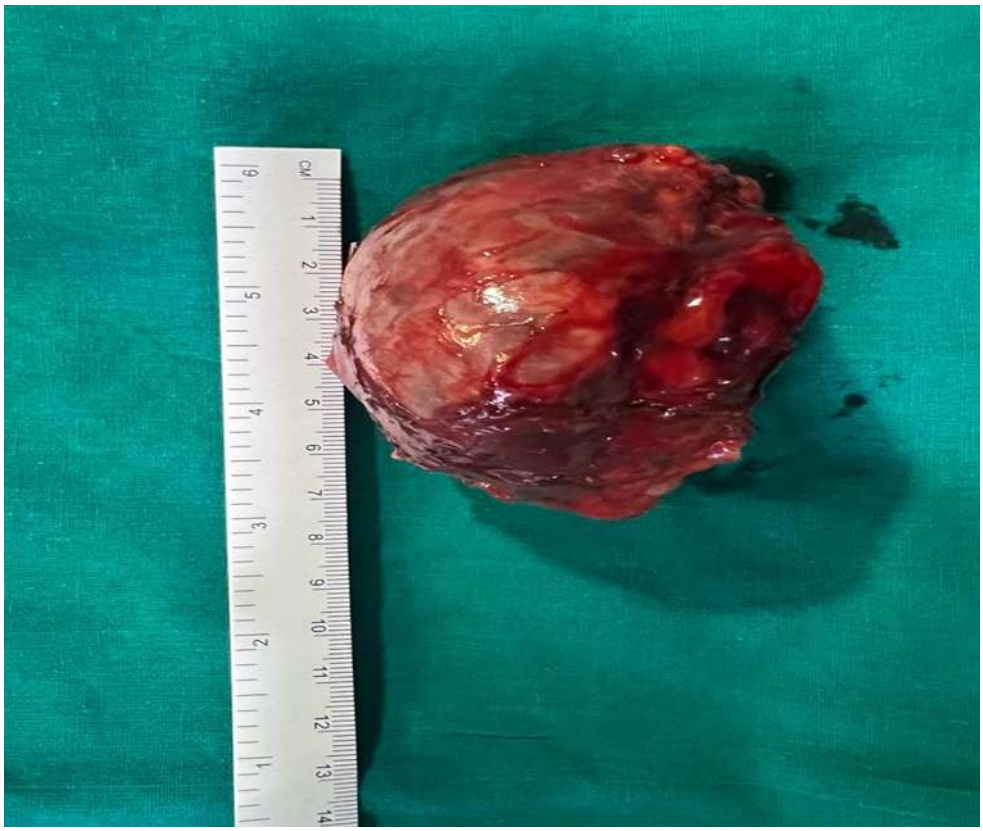

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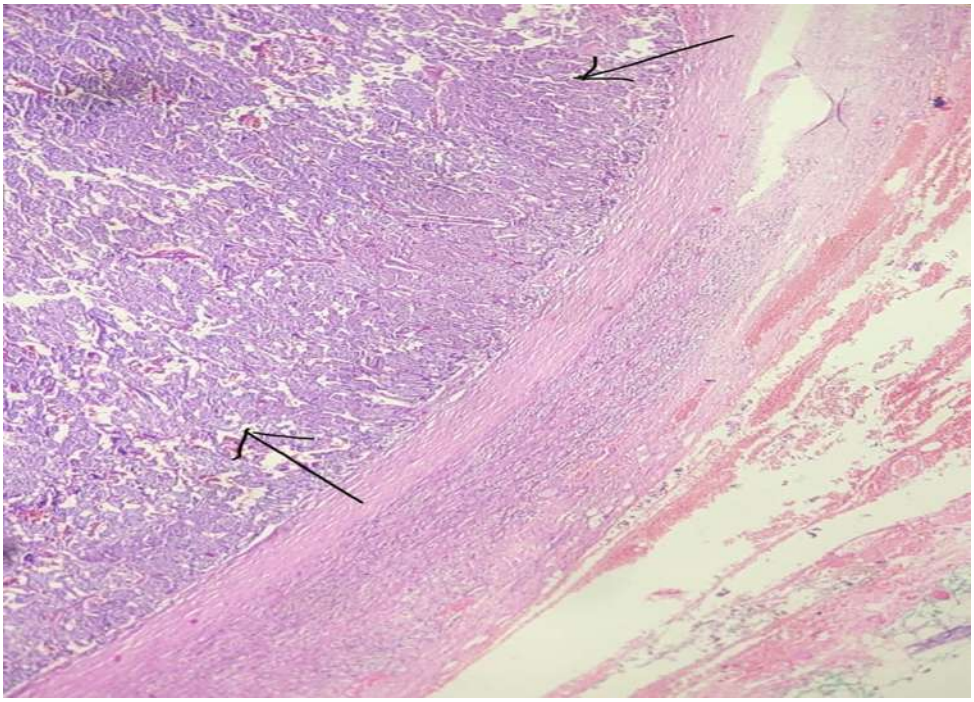
FIGURE 8- Histopathological section revealed a well circumscribed neoplasm composed of neoplastic cells arranged in zell-ballen pattern and trabecular pattern. Individually the neoplastic cells are large, polygonal with granular cytoplasm. Nuclei is oval and uniform with prominent nucleoli. No capsular and vascular, adrenal adipose invasion seen without mitotic activity. The lesion is surrounded by compressed rim of adrenal cortex and fibrotic tissue. (Arrow marked section). Rest normal adrenal tissue seen.



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