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MANAGEMENT OF SILENT CYSTIC PHEOCHROMOCYTOMAS WITH BENIGN OR MALIGNANT HISTOLOGY

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Abstract

Introduction. The differential diagnosis of abdominal cystic lesions should include investigation of cystic pheochromocytomas. To date only a few cases of purely cystic pheochromocytoma have been reported in the English literature.

Aim. To present the management in four cases of silent pheochromocytomas patients who presented with pure or partially cystic abdominal lesions with benign (n:3) and malignant characteristics (nonspecific neuroendocrine tumor) (n:1) in histological evaluation.

Results. Resection of the tumor is considered the primary treatment option in the management of pheochromocytoma, and preoperative preparation with alpha and beta antagonists is crucial in order to avoid precipitation of hypertensive crisis during surgical procedures. The absence of clinical symptoms and lack of typical radiological features may complicate the diagnosis of pheochromocytoma resulting with increased mortality and morbidity during surgery.

Conclusion. Asymptomatic pheochromocytomas are rare and they are responsible for approximately 5% of adrenal incidentalomas. These lesions may be referred to surgery as clinically nonfunctional adrenal adenomas.

Key words: pheochromocytoma, alpha antagonists, surgery.

INTRODUCTION

Pheochromocytomas are usually round or oval shaped, well - marginated lesions which are generally measured larger than 3 cm in radiological studies. These lesions are highly vascular, and are prone to hemorrhage and necrosis when they present with larger sizes. Pheochromocytoma lesions are usually bright on T2 - weighted images with magnetic resonance imaging (MRI). MRI can also identify the presence of tumor thrombus in the IVC or renal vein, during the planning of the extent of resection (1). Computed tomography (CT) and meta-iodo-benzyl-guanidine (MIBG) scans are complementary studies for localizing these tumors.

Cystic pheochromocytomas are unusual variants of adrenal pheochromocytomas and they may be the result of hemorrhage and necrosis of an adrenal pheochromocytoma. Occasionally there may be some difficulties with the diagnosis as they can be confused with cystic lesions of adjacent structures such as kidney or pancreas and may mimic malignant lesions. Pheochromocytoma differs from other adrenal tumors by catecholamine secretion which is responsible for the typical signs and symptoms such as hypertension associated with palpitations, headache and diaphoresis (2). They are rarely malignant and tend to be larger in size when malignancy is present (3). The presence of radiological findings like invasion of contiguous organs and vascular structures may be an indicator of malignancy (2, 3). Initial screening for elevated levels of plasma or 24-hour urine catecholamines and their metabolites is appropriate. However, in purely cystic pheochromocytomas, patients may be asymptomatic and there may not be any elevation in the urinary or plasma levels of catecholamine metabolites (4, 5).

Cystic pheochromocytomas may present with gastrointestinal symptoms, abdominal or lumbar pain, or they can manifest themselves as palpable masses in the abdomen. Resection of the tumor is considered as the primary option for the treatment. As there is a risk of hypertensive crisis during surgery, due to elevated catecholamine secretion, preoperative preparation with alpha - adrenergic blockade is essential, once a diagnosis of functioning pheochromocytoma has been established. If tachycardia develops during medical preparation with alpha- blocker treatment, beta-adrenergic blocking agents are added to the treatment after normalization of hypertension (3). We herein present our clinical experience with four pheochromocytoma patients who had pure cystic (n: 2) or partially cystic adrenal lesions (n: 2) and were referred to our department due to the complications that occurred during their management.

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CASE 1

A 50 - year - old woman was admitted to the emergency department with abdominal pain and distension. A huge, predominantly cystic abdominal mass of 20x16 cm which occupied a large part of the left superior abdominal cavity was detected (Fig. 1). Surgery was performed with suspicion of pancreatic pseudocyst. During the surgical procedure, acute hypertensive crisis occurred and the operation was terminated just after a biopsy of the lesion was obtained. Hypertensive attack was managed with nitroprussid infusion. Later she was referred to our department for further evaluation. The laboratory results revealed extremely high urinary metanephrine (M) and normetanephrine (NM) levels (Table 1, with normal reference ranges of M and NM). Urinary catecholamine levels were measured with LC-MS/MS method and ZIVAK Tandem MS analyzer was used. The patient denied use of tricyclic antidepressants, decongestants, levodopa, amphetamines and ethanol ingestion in the last two weeks which were questioned before the measurement of urinary catecholamine levels in order to eliminate false positive results. The pathological examination of the biopsy was compatible with pheochromocytoma. Doxazosin and Amlodipine treatment was initiated. Plasma cortisol, dehydroepiandrosterone, and electrolyte levels were normal. Additional hormonal tests were performed to rule out MEN syndromes including plasma glucose, ionized calcium, intact parathyroid hormone, calcitonin and these were detected in the normal reference ranges. Meta-iodo-benzyl-guanidine 123-I (MIBG) scintigram showed only minimal uptake at solid components of the tumor with a ring shaped contrast enhancement (Fig. 2). The patient was consulted with Endocrine Surgery Department and the lesion was considered as inoperable. Medical treatment with alpha adrenergic receptor blocker (Doxazosin 16 mg/day, Phenoxybenzamine 120 mg/day) and calcium channel antagonist (Amlodipine 20 mg/day) was initiated. The large size of the tumor led us to reevaluate the possibility of surgical intervention and the patient was consulted with a different surgical team for a second opinion. On the fourteenth month of Doxazosin, Amlodipine and Phenoxybenzamine treatment, CT-

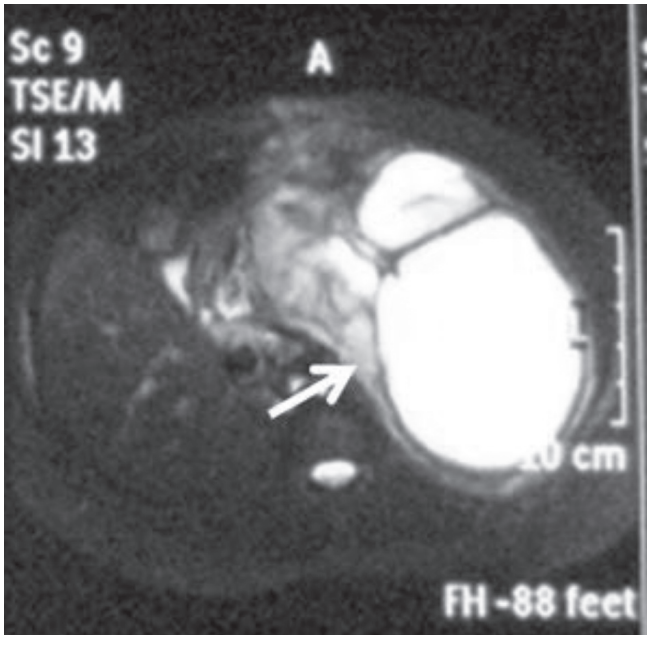

Figure 1. MRI Axial T2- weighted image of cystic lesion on the left adrenal.

Table 1. Clinical features of the cases

	Case 1	Case 2	Case 3	Case 4
Age	50	50	42	44
Gender	Female	Male	Male	Female
BP (mmHg)	210/120	180/130	220/110	190/100
Initial diagnosis	Pseudocyst	Adrenal cyst	Adrenal cyst	Hydatic cyst
Tumour site	Left	Right	Right	Right
Tumour size (cm)	20	5	6	12
UCL* (µg/day) **NM:88-444 µg/day** **M:52-341 µg/day**	NM∞: 30718 Mγ: 15076	NM:1186 M: 2309	NM: 10010 M: 3500	NM: 14000 M: 10800
Ki-67 score (%)	1	3	N/A	%30
F/U¥ (months)	24	30	36	96
Recurrence/Metastasis	-	-	-	+/+

*UCL: Urinary catecholamine levels ,
∞NM: Normetanephrine, γM: Metanephrine
¥F/U: Follow Up Time

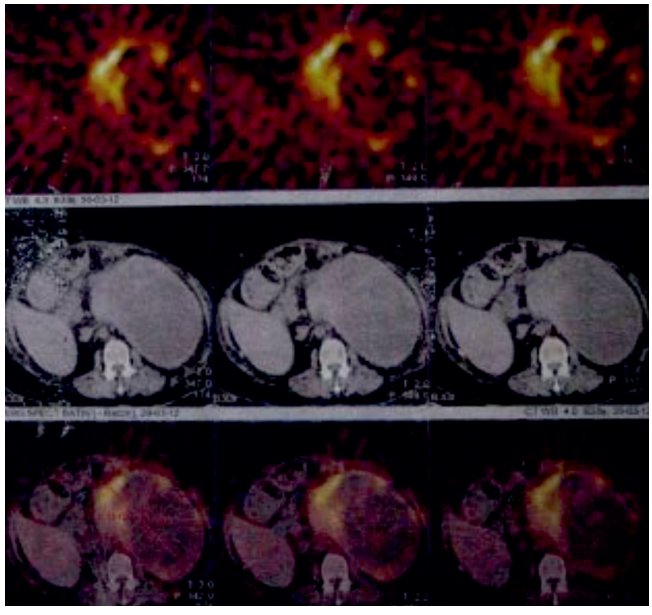

Figure 2. Ring shaped contrast enhancement on 123-I MIBG scintigram.

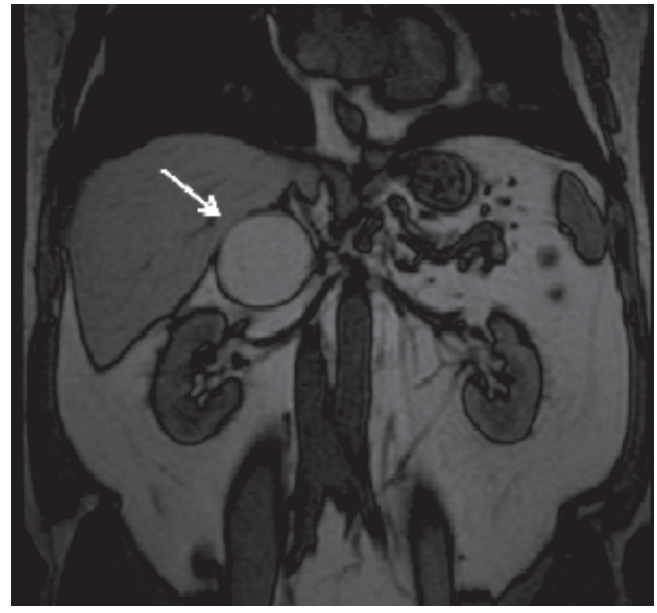

Figure 3. A right sided hyperintense cystic lesion on T2 weighted MRI image.

angiography was performed uneventfully, and no sign of vascular invasion was detected. The patient was transferred to Endocrine Surgery Department. Tumor resection was completed with distal pancreatectomy and splenectomy due to the adhesions of the lesion to the surrounding tissues. Surgery was performed without any complication. The pathological evaluation revealed 20x18 cm cystic pheochromocytoma lesion with capsule and minimal soft tissue invasion and Ki-67 score was 1%. The immunohistochemistry evaluation showed chromogranin A and synaptophysin positivity. Urinary catecholamine levels decreased to normal levels four weeks after the surgery and her blood pressures are under control with lower doses of Doxazosin (4 mg/day) and Amlodipine (5mg/day) treatment. The patient is being followed up periodically with urinary catecholamine levels and abdomen MRI for the detection of possible local recurrence and distant metastasis.

CASE 2

A 50 year old male was referred to our department with signs and symptoms of pheochromocytoma accompanied by hypertensive attacks which had started two months ago. He had been diagnosed with coronary heart disease for seven years. On physical examination his blood pressure was 230/130 mmHg, multiple neurofibromas and café-au-lait macules were recorded. Abdominal MRI revealed a right sided 50x44 mm cystic lesion which was hypointense on T1 weighted images; and hyperintense on T2 weighted images. Urinary catecholamine levels were 5 folds over the upper limit of reference ranges (Metanephrine: 52-341 µg/day, Normetanephrine: 88-444 µg/day, Table 1). Clinical and laboratory findings were compatible with Neurofibromatosis Type 1 and adrenal pheochromocytoma. I -123 MIBG scintigram showed a peripheral halo surrounding the adrenal mass. After normalization of hypertension with Doxazosin 12 mg and Amlodipine 5 mg, Propranolol 30 mg was added to the treatment and right adrenalectomy was performed successfully after three months of medical preparation. Histopathological examination revealed pheochromocytoma, with diffuse necrotic areas and tumor capsule invasion. Ki-67 proliferation index was 2-3%. Urinary catecholamine and metanephrine levels decreased to normal levels three months after the surgery. He has been followed up under remission with normal urinary catecholamine levels and blood pressure is under control with Doxazosin (4 mg/day) treatment.

CASE 3

A 42 year old male was referred to our department for further evaluation of pheochromocytoma with symptoms of paroxysmal headache, palpitation and hypertension. On physical examination his blood pressure was 220/120 mmHg. Abdomen MRI revealed a six cm right adrenal mass (Fig. 3) and the 24 hour urinary metanephrine and normetanephrine levels

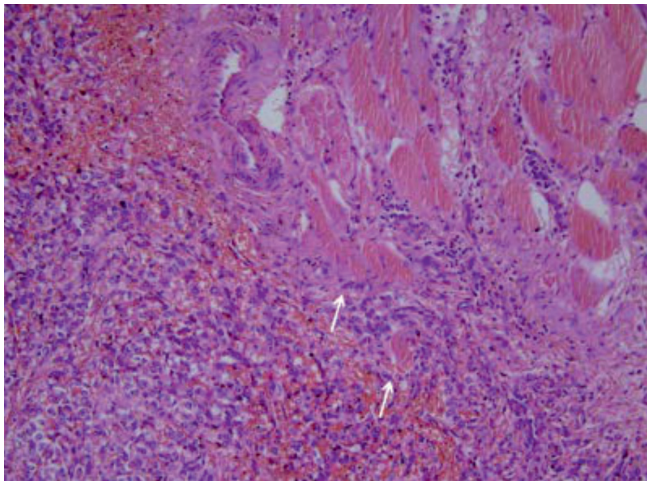

Figure 4. Surrenal resection of Case 4, revealed gross invasion of the diaphragma (Arrow). Tumor cells with eosinophilic cytoplasm and round vesicular nuclei were arranged in well-defined nests (H&E, 20X).

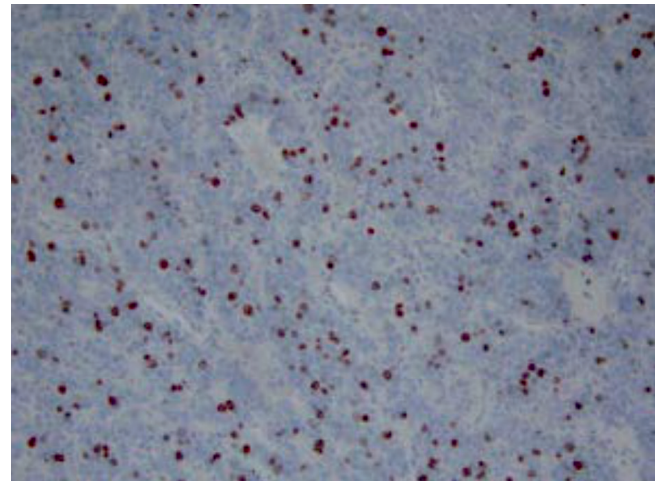

Figure 5. High proliferative activity with MIB-1 was observed in the tumor cells and Ki67 proliferation index was 30 % (20X).

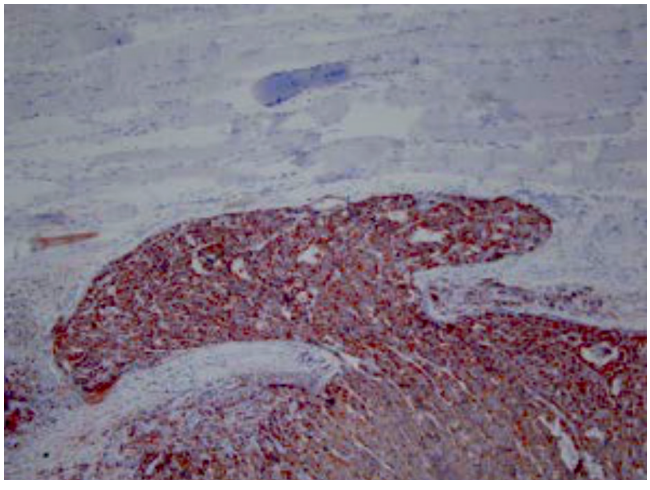

Figure 6. Tumor cells showed intense immunoreactivity for Chromogranin A (20X).

were significantly elevated by 20 folds over the upper limit of the normal range (Table 1). Other laboratory tests which were performed in order to exclude diagnosis of multiple endocrine neoplasia including calcitonin, parathyroid hormone, ionized calcium and glucose levels were normal. Medical treatment with Phenoxybenzamine 40 mg/day, Amlodipine 5 mg/day and Propranolol 40 mg/day was performed for two months before adrenalectomy. Surgery was successful without any complications. Pathological examination, revealed a seven cm pheochromocytoma with multiple cystic degeneration areas. The lesion was partially encapsulated with absence of capsular or vascular invasion. The surrounding cortex showed micronodular hyperplasia. Blood pressure and 24 hour urinary metanephrine, normetanephrine levels returned to normal one month after the surgery. Abdomen MRI and urinary catecholamine levels which were detected in normal ranges were used during the follow-up of possible local recurrence and distant metastasis.

CASE 4

A 44 year old female was admitted to emergency department with abdominal pain and a giant palpable lesion on the right side of the abdomen. Abdomen MRI revealed a 12 cm cystic lesion on the right adrenal region and abdominal surgery was performed with suspicion of a hydatid cyst. Due to sudden hypertensive crisis which occurred during anesthesia induction, the operation was terminated immediately and she was referred to our department for further evaluation of pheochromocytoma. Her medical history was remarkable for symptoms of palpitation, hyperhidrosis and headache accompanied by hypertensive episodes. She had been experiencing these symptoms for the last three years. The 24 hour urinary catecholamine levels were elevated more than 30 folds above the upper range (Table 1). Diagnosis of pheochromocytoma was made and right adrenalectomy was performed uneventfully after two months of preoperative medical therapy with Doxazosin 12 mg, Phenoxybenzamine 60 mg and Amlodipine 10 mg. Pathological evaluation revealed cystic pheochromocytoma with features of borderline malignancy due to high proliferation index (Ki67 score 30%) and diaphragm invasion (Figs 4-6). Immunohistochemical staining revealed presence of eosinophilic cytoplasm and round vesicular nuclei arranged in well-defined nests and chromogranin-A staining which was also compatible with the diagnosis. The disease recurred six times locally. Surgery was the

first choice in the management of operable lesions but when the lesions were inoperable, 123-I MIBG therapy was performed. Occipital lobe metastasis was detected on the seventh year of the follow-up period. Patient died 6 months after the resection of occipital lobe metastasis.

The patients' clinical features are summarized in Table 1.

DISCUSSION

The differential diagnosis of cystic adrenal lesions includes adrenal hydatid cysts, pseudocysts, adrenal carcinoma, and cystic pheochromocytoma (6). About one third of pheochromocytomas have some cystic component, however there are only a few case reports of pure cystic pheochromocytomas in the literature (4, 7, 10). Furthermore, nearly half of these cases are referred to as clinically silent pheochromocytoma . Absence of classical signs and symptoms may complicate the preoperative diagnosis of pheochromocytoma, resulting in life threatening hypertensive crisis during abdominal surgery due to the lack of adequate preoperative medical preparation (4, 7, 11). Abdominal mass or pain may be the only clinical findings with absence of classical pheochromocytoma symptoms. Therefore these lesions may easily be confused with the giant cystic neoplasms of adjacent structures such as liver, pancreas or spleen (4, 7).

Several explanations are predicted for clinically silent pheochromocytoma lesions. One theory is that extensive necrosis in the cystic region may result with a decrease in the number of catecholamine producing cells. Cystic degeneration may be very prominent, and sometimes only a few identifiable cells may remain in a thin margin that serves to disclose the true nature of the lesion as seen in Case 2. Another possibility is that the interstitial tissue without bioactivity may be the main component of the neoplasm resulting with decreased catecholamine secretion.

In cystic pheochromocytoma lesions, most of the catecholamine and their metabolites may be stored in the capsular mass and may infuse intravenously into the circulation during the manipulation of the mass, which may be responsible for the precipitation of hypertensive crisis in surgical procedures (12). In the first case (Case-1) presented above, the patient was operated with a diagnosis of pancreas pseudocyst and pheochromocytoma was not suspected due to lack of classical symptoms. This failure in diagnosis resulted with hypertensive crisis during the surgical procedure. The larger size of cystic adrenal masses presenting without classical signs and symptoms of pheochromocytoma should not rule out the possibility of clinically silent pheochromocytoma; and plasma or urine metanephrines should always be performed in the initial biochemical evaluation of these lesions (5).

Pheochromocytomas are quite vascular lesions and they frequently manifest with focal or partial cystic degeneration. However, total or subtotal cystic degeneration of pheochromocytomas is not common. There have been a few reports in the literature describing totally cystic tumors (6). It has been suggested that the process starts with intraparenchymal hemorrhage followed by necrosis; and the areas of necrosis later undergo resorption. The triggering mechanism is thought to be the tumor outgrowing its vascular supply (6). Presence of necrosis and liquefaction within pheochromocytoma lesions results with formation of cystic components within the tumor. According to one series, 32% of the pheochromocytomas studied with US were cystic or had cystic components (3). In a study performed with 41 patients who had cystic adrenal lesions, three of the patients had pheochromocytoma (4).

Hemorrhage or degeneration within a pheochromocytoma may result in a pseudocyst (4) formation which may be confusing in clinically silent pheochromocytoma patients. After biochemical confirmation of the diagnosis, pheochromocytoma should be localized with MRI. When non-invasive techniques fail to localize the tumor and evaluate its vascular structure, invasive techniques may be necessary. Angiography contributes significant information in the preoperative evaluation of patients suspected of harboring a pheochromocytoma (5). However, it should be kept in mind that there are some theoretical concerns about administering iodinated contrast material to a patient with pheochromocytoma as this may trigger malignant hypertension when it is performed without adequate medical preparation. Despite reassuring reports of studies performed with low-osmolar nonionic contrast agents (Iopamidol, Iohexol, Iopromide) (6), current accepted practice would generally avoid the use of iodinated contrast material (High osmolar contrast media; HOCM, Diatrazoate, Iothalmate, Iodamide) in a patient with a diagnosis of pheochromocytoma. However, there are some studies implicating that preprocedural preparation with phenoxybenzamine and the use of less toxic contrast media may prevent a spontaneous adrenergic crisis during the procedures that are performed with iodinated contrast material. Therefore, arteriography is

considered a safe and useful procedure for localization and vascular evaluation of pheochromocytomas when it is performed after medical preparation (7). However, there are no standard recommendations about the time and duration of the medical preparation. On the other hand, CT – angiography that is performed with non-ionic contrast media is safer for these patients in order to avoid hypertensive crisis. The first patient presented here (Case-1) had been receiving alpha blocker treatment for 14 months before the CT angiography was performed and hypertensive attack was not noted during the procedure.

Radioscintigraphy may also help in localization of the primary tumor or secondary lesions by using Iodine-131 metaiodobenzylguanidine (MIBG) which is an analogue of guanethidine that competes with norepinephrine at synaptic reuptake receptors. In catecholamine producing masses, there is increased uptake of this radiopharmaceutical. The sensitivity of use of I-131 MIBG to visualize pheochromocytoma is 85% with a specificity of 96% (8). The advantage of radioscintigraphy is the ability to survey the entire body and localize extra adrenal lesions.

The definitive treatment of pheochromocytomas is surgical excision. Preoperatively, these patients should undergo adrenergic blockade to avoid complications from release of catecholamine during surgery. Alpha-adrenergic receptor blockers are recommended as the first choice. Initiation of beta - adrenergic receptor blockers is indicated to control tachycardia only after administration of alpha-adrenergic receptor blockers. Use of beta-adrenergic receptor blockers in the absence of an alpha-adrenoceptor blocker may trigger hypertensive crisis due to unopposed stimulation of alpha-adrenergic receptors (8). In Case 1, the tumor was considered as inoperable at first and medical treatment was initiated. But the large size of the tumor led us to reevaluate the possibility of surgical intervention which would definitely improve the patient's quality of life and surgery was performed uneventfully after medical treatment. Minimally invasive (laparoscopic) adrenalectomy is recommended for most of the adrenal pheochromocytomas especially which are small and noninvasive (8). Laparoscopic adrenalectomy remains the first choice in the treatment of cystic pheochromocytomas as well, but special attention must be paid during the procedure in order to avoid fragmentation of adrenal tissue, and cyst rupture which would result with subsequent intra-abdominal fluid spillage (9). Therefore laparoscopic adrenalectomy which is also known to be associated with less pain, and less surgical morbidity than open adrenalectomy (8) was performed in Case 2 and Case 3 without any complications. However, in the remaining patients (Case 1 and 4) the large size of the pheocromocytoma lesions made open surgery obligatory in order to ensure complete resection and avoid tumor rupture.

Generally, tumor sizes greater than 6 cm are malignant. Goldstein and colleagues found that it was very difficult to predict the biological behavior of pheochromocytoma by histopathological evaluation (12). As with other neuroendocrine tumors, the diagnosis of malignancy in pheochromocytoma lesions is defined by the presence of local invasion or metastatic disease (2, 3) and approximately 13% of pheochromocytomas are malignant (11). Common sites of metastases are the axial skeleton, liver, lungs, and retroperitoneal or mediastinal lymph nodes. The 5-year survival rate with malignant pheochromocytoma is less than 50% (19). Malignant pheochromocytoma lesions tend to be larger and they may also exhibit some findings such as calcification, hemorrhage, necrosis and cystic degeneration. Although cystic degeneration may be an indicator of malignancy in these lesions, an exact calculation of incidence may be difficult due to the rarity of cystic pheochromocytomas. Apart from tumor size, postoperative persistence of arterial hypertension after the removal of the lesion is more frequently related with malignancy (20).

In purely cystic pheochromocytoma patients the classical symptoms may not always be present and this may complicate the preoperative diagnosis. Therefore, preoperative evaluation of plasma or urinary catecholamine levels is essential before the surgical management of cystic retroperitoneal lesions. All patients with a hormonally functional pheochromocytoma, should receive preoperative adrenergic receptor blockade for 7 to 14 days to prevent cardiovascular complications. Blood pressure, heart rate, and glucose levels must be monitored in the early postoperative period. Plasma or urine levels of metanephrines should be checked in order to evaluate persistent disease and annual biochemical testing is recommended in the evaluation of recurrent or metastatic disease. The huge size of these lesions does not always implicate inoperability and reevaluation with CT angiography may be useful in patients who were diagnosed as inoperable at the first clinical assessment. These procedures may be helpful in the decision of surgical treatment which significantly improves the mortality and morbidity of pheochromocytoma patients.

In conclusion, it is essential that pure cystic

pheochromocytomas should be considered in the differential diagnosis of intra-abdominal cystic lesions by performing a careful and detailed medical history, clinical evaluation and cathecholamine biochemistry before the decision of surgery is made.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

References

1. Gray DK, Thompson NW. Pheochromocytoma. Surgical endocrinology. Lippincott Williams & Wilkins, Philadelphia; 2001, 247-262.
2. Landsberg L, Young JP. Pheochromocytoma. Harrison's principles of internal medicine. 15th ed. New York: McGraw-Hill; 2001, 2105-2109.
3. Norton AJ. Adrenal Tumors, Pheochromocytoma. Cancer: principles and practice of oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005, 1770-1778.
4. Antedomenico E, Wascher RA. A case of mistaken identity: giant cystic pheochromocytoma. Curr Surg. 2005; 62(2): 193-198.
5. Radojkovic D, Stojanovic M, Pesic M, Radojkovic M, Radenkovic S, Radjenovic TP, Stevic M, Stankovic I. Clinically "Silent" Giant Pheochromocytoma. Case Report. Acta Endocrinologica-Bucharest 2013; 9(1):121-129.
6. Klingler PJ, Fox TP, Menke DM, Knudsen JM, Fulmer JT. Pheochromocytoma in an incidentally discovered asymptomatic cystic adrenal mass. Mayo Clin Proc 2000; 75(5):517-520.
7. Wu JS, Ahya SN, Reploeg MD, Singer GG, Brennan DC, Howard TK, Lowell JA. Pheochromocytoma presenting as a giant cystic tumor of the liver. Surgery 2000; 128(3):482-484.
8. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF, Jr. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99(6):1915-1942.
9. Cavallaro G, Crocetti D, Paliotta A, De GA, Tarallo MR, Letizia C, De TG. Cystic adrenal lesions: Clinical and surgical management. The experience of a referral centre. Int J Surg 2015; 13:23-26.
10. Minei S, Yamashita H, Koh H, Satoh T, Kobayashi S, Furuhata M, Uchida T, Baba S. [Giant cystic pheochromocytoma: a case report]. Hinyokika Kiyo 2001; 47(8):561-563.
11. Gonzalez RJ, Lee JE. Adrenal Tumors. The M.D. Anderson surgical oncology handbook. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006, 419-439.
12. Li C, Chen Y, Wang W, Teng L. A case of clinically silent giant right pheochromocytoma and review of literature. Can Urol Assoc J 2012; 6(6):E267-E269.
13. Schwerk WB, Gorg C, Gorg K, Restrepo IK. Adrenal pheochromocytomas: a broad spectrum of sonographic presentation. J Ultrasound Med 1994; 13(7):517-521.
14. Erickson LA, Lloyd RV, Hartman R, Thompson G. Cystic adrenal neoplasms. Cancer 2004; 101(7):1537-1544.
15. Tisnado J, Amendola MA, Konerding KF, Shirazi KK, Beachley MC. Computed tomography versus angiography in the localization of pheochromocytoma. J Comput Assist Tomogr 1980; 4(6):853-859.
16. Mukherjee JJ, Peppercorn PD, Reznek RH, Patel V, Kaltsas G, Besser M, Grossman AB. Pheochromocytoma: effect of nonionic contrast medium in CT on circulating catecholamine levels. Radiology 1997; 202(1):227-231.
17. Baid SK, Lai EW, Wesley RA, Ling A, Timmers HJ, Adams KT, Kozupa A, Pacak K. Brief communication: radiographic contrast infusion and catecholamine release in patients with pheochromocytoma. Ann Intern Med 2009; 150(1):27-32.
18. Swensen SJ, Brown ML, Sheps SG, Sizemore GW, Gharib H, Grant CS, van Heerden JA. Use of 131I-MIBG scintigraphy in the evaluation of suspected pheochromocytoma. Mayo Clin Proc 1985; 60(5):299-304.
19. Gonzalez RJ, Lee JE. Adrenal Tumors. The M.D. Anderson surgical oncology handbook. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006; 419-439.
20. Bravo EL, Tagle R. Pheochromocytoma: state of the art and future prospects. Endocr Rev. 2003;24(4):539-553.