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Asymptomatic Pheochromocytoma Interpreted as Non-Functioning Incidentaloma: A Major Challenge: Case Report and Review

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Abstract

Introduction

Adrenal incidentaloma (AI) is a result of easy availability of imagiological diagnostic techniques and may include many primary, metastatic, benign, and malignant entities, the majority of which are benign and nonfunctioning adrenal adenomas. However to 7% prove to be pheochromocytomas.

Case Report

38 year old male with right adrenal adenoma associated co-morbidity was pre-diabetic without symptoms suggesting pheochromocytoma, biochemically with a borderline increase on urinary norepinephrine. He was proposed for laparoscopic right adrenalectomy with no preoperative pharmacological preparation. Intra operatively, the tumor manipulation resulted in manifestations typical of pheochromocytoma, refractory to treatment, with biochemical signs of myocardial ischemia.

Discussion

Usual recommendations are on favor of measuring plasma and urinary fractionated metanephrines in all patients with adrenal incidentaloma, this evaluation should be complemented with imagiological findings. There is no universal consensus on when to start preoperative preparation, in which patients or which pharmacological scheme should be used.

Conclusion

Based upon ours and reported experience, we recommend that every asymptomatic patient with adrenal mass and biochemical evaluation suggestive of pheochromocytoma should be preoperatively submitted to alpha-antagonism to avoid potentially life threatening hemodynamic fluctuations on intraoperative and postoperative period.

Introduction

Adrenal incidentaloma (AI) is a term used to classify adrenal masses that are discovered incidentally, after an imaging procedure not related to the adrenal gland [1]. Usually, the patient is asymptomatic and has no signs of hormonal excess or obvious underlying malignancy [2]. Its prevalence is rising as a result of easy availability of imagiological diagnostic techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). A study reported a prevalence of adrenal incidentaloma on abdominal CT of 4.4% [3]. The differential diagnosis of AI includes many primary, metastatic, benign, and malignant entities, the majority of which are benign and nonfunctioning adrenal adenomas [4]. Factors influencing transformation of a truly non-functioning incidentaloma into a hypersecretory or a malignant tumor are not entirely known [5]. Approximately 3-7% of AI proves to be pheochromocytomas [6-8].

Until recent years, it was thought that all patients with pheochromocytoma are symptomatic. However, with widespread use of computed imaging, pheochromocytomas are being discovered in the presymptomaticstage [8,9]. Although some recommend measurement of plasma fractionated metanephrines in all patients with adrenal incidentaloma, others suggest this measurement only when the pre-test probability of pheochromocytoma is high (eg., if the mass is vascular, dense, and has slow contrast washout), because while this test is very sensitive (95 to 98 percent), it is not very specific (89 to 95 percent) [10].

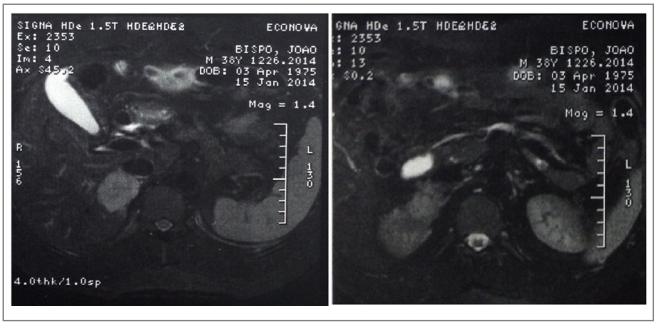
Laparoscopic adrenalectomy has become the standard approach in the management of adrenal mass [11]. This technique is minimally invasive and has the advantage of decreasing convalesces, less postoperative pain, and blood loss with improved cosmesis.

There are no clear recommendations in contemporary literature as to the pre-operative preparation of non-secretory, asymptomatic incidentaloma in normotensive individuals with normal biochemical and endocrinological profile.

We report an unusual case of undiagnosed pheochromocytoma on a normotensive patient, presenting an intra-operative management problem.

Case Report

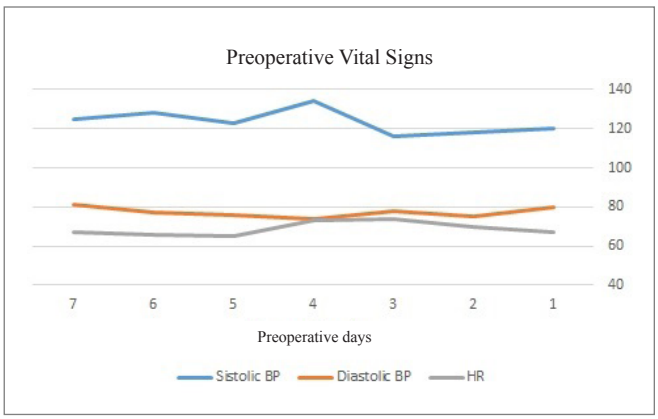
38 year old male, presenting with diffuse and intermittent abdominal pain. For that reason, an abdominal CT scan was performed and revealed a right adrenal adenoma with 5,3x3,8 mm round shape, smooth contour with sharp margin with compression effect on inferior vena cava. MRI revealed an adrenal mass with 5,8x5,7x4,6 cm, slightly hyperintense on T2 with slow washout pattern (Figure 1). As associated co-morbidity was recently diagnosed pre-diabetes controlled with diet and appendectomy 5 years ago. There was no history of allergies and no regular medication. Clinically there weren´t any complaints of episodic headaches, palpitations, sweating, chest pain, or hypertension. There was no history of weight gain, excess hair growth on the body, acne or proximal muscle weakness. No previous history of hypertension, weakness, anorexia, vomiting, abdominal pain, fever, diarrhea, polyuria, or polydipsia could be elucidated.



On examination, patient's pulse rate was 65bpm, blood pressure (BP) was 130/70 mmHg, without any postural drop, and respiratory rate was 14cpm. His height was 181 cm, and his weight was 82 kg. No evident edema. There was no evidence of moon facies, hirsutism, acne, purple abdominal striae, *Acanthosis nigricans*, or knuckle or mucosal pigmentation. The rest of the examination was unremarkable. He was classified as an ASA 2 preoperatively.

On laboratory evaluation performed, the only changed value was a borderline increase on urinary norepinephrine (99,8mcg/24hrv 80,2 mcg/24h) but urinary metanephrines were negative.

Chest radiography and electrocardiogram were normal. Pre-operative vital signs are described in Figure 2.



The mass was considered non-functioning and patient was proposed for laparoscopic right adrenalectomy with no preoperative pharmacological preparation.

Intraoperatively, ASA standard monitoring was connected, patient preoxygenated with 100% O_2 by face mask followed by induction of anesthesia using Fentanyl 150 mcg, propofol 250 mg, and Rocuronium 50 mg. Mask ventilation and intubation were uneventful. Inhaled sevoflurane 3.5% was used initially. A left radial arterial line was placed for invasive monitoring of BP. Central venous pressure was not monitored. The patient was positioned in left lateral position with pressure points padded. Patient vital signs remained stable until tumor laparoscopic manipulation started. Suddenly patient BP started to rise reaching 290/140. It remained uncontrollable even after frequent boluses of esmolol and IV infusion of isosorbidedinitrate and sodiumnitroprusside.

The tumor was of difficult access and, after 3 hours of laparoscopy, it was converted to lumbotomy. BP kept of difficult control even with the triple IV therapy referred and blood glucose level ranged from 230-270 resistant to IV insulin boluses administered.

During the procedure, the cardiac monitoring revealed frequent ventricular extrasystoles and, at some point during de tumor ressection, continued ventricular extrasystoles as documented in Figure 3. Lidocaine was administered with stabilization of ECG tracing. Troponin assay was requested.

The mass was adherent to the vena cava and at certain time during the surgery there was a need to block venous return (Inferior Vena Cava clamp). At this moment BP decreased to 50/30 mmHg and IV fluid challenge was performed and ephedrine administered. 1 unit of packed red blood cells and 1 unit of fresh frozen plasma were administered, as well as 4g of fibrinogen in consonance with intraoperative thromboelastogram. After tumor removal, BP stabilized at 90-110 systolic and 50-70 diastolic. No amine infusion was needed to maintain MAP.

The intraoperative vital signs fluctuation is described in Figure 4. The intraoperative acid base balance is described in Table 1.

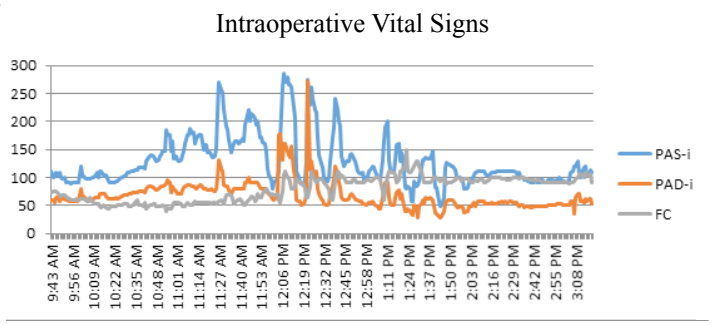


Table 1	Hours	
	12:37PM (FiO2 = 43%)	14:30PM (FiO2 = 51%)
pH	7,18	7,16
pCO2	49,5	51,5
pO2	297	322
HCO3	16,5	16
Lac	65	42
K+/Na+	2,9/145	3,4/143
Hb	12,3	14,6
Glic	255	237

Urine output was 1 – 1,75 ml/kg/h.

Patient was awakened and could be extubated uneventfully, and was transferred to Post-anesthetic care Unit.

Postoperatively, the patient kept MAP above 60 mmHg and HR 60-70 bpm with no need of amine infusion. Troponins were positive at 4 and 6 hours post-op and serial electrocardiograms were innocent. No chest pain was reported.

He was discharged to ward after 2 days. The tumor histological examination revealed pheochromocytoma. Patient was discharged after 1 week of the procedure to be followed at the outpatient clinic.

Discussion

This case report is an obvious demonstration of the importance of differential diagnosis on adrenal incidentalomas. We discuss a case of a pheochromocytoma interpreted as a non-functioning incidentaloma that presented with an intra-operative challenging hypertensive crisis.

Although, in general, the majority of adrenal incidentalomas are nonhypersecretory adenomas, hormonal screening evaluation can reveal a significant number of cases of clinically unsuspected hormone-secreting adrenal tumors [12]. The two main concerns with regard to an adrenal incidentalomas are whether it is hormonally active or malignant. So careful personal and family history, review of systems, and physical examination should be performed in all patients, even when asymptomatic [13]. Pheochromocytoma is completely asymptomatic in up to 15% of cases [14]. Evaluation from Endocrinology is required in all patients with adrenal incidentalomas.

In this case, the slightly increased urinary norepinephrine and the characteristics (dimension and slow washout pattern) on MRI could suggest the necessity of preoperative pharmacological preparation (raised suspicion of malignant lesion).

Usual recommendations are on favor of measuring plasma and urinary fractionated metanephrines in all patients with adrenal incidentaloma [15]. Nevertheless, this test is very sensitive (95 to 98 percent), but not very specific (89 to 95 percent). So one should endeavor imagiological evaluation. If the mass detected on CT scan is vascular, dense, and has slow contrast washout this raisessuspicion ofpheochromocytoma and preoperative preparation with alpha blockers is suggested to be necessary, even if the patient is asymptomatic, to avoid intraoperative problems [7]. However, this suggestion is controversial [16].

There are no perfect recommendations for management of asymptomatic AI. However, the question is: what tests should anesthesiologists insist upon prior to taking such patients to the operating room? The lack of decision models

on preoperative evaluation asymptomatic AI led us to present a decision tree based on current information [12-15] (Figure 5). This chart differs from the ones presented in Endocrinology and Anesthesiology reunions on the following points:

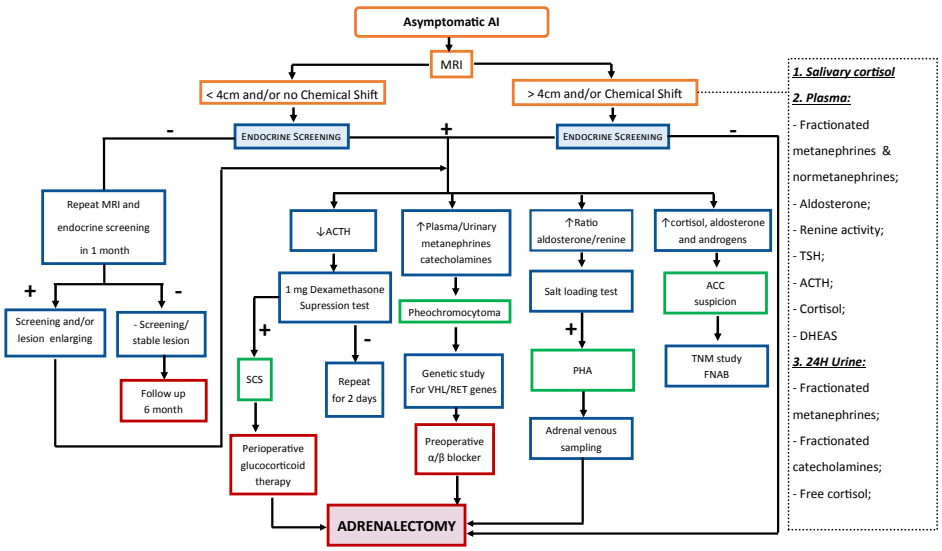
• The importance of preoperative MRI even if previous echography or CT-scan were performed: chemical shift imaging can be used to diagnose adrenal cortical adenomas with 81-100% sensitivity and 94-100% specificity [17]. Moreover, the sensitivity is lower but still acceptable for lipid-poor adenomas;

• An endocrine screening should be performed even with an innocent MRI;

• If endocrine screening is negative it should be repeated in one month to minimize false negatives. We also recommend that preoperative endocrine screening should be no longer than one month old. On the case presented above the preoperative endocrine screening was 3 month old and with another screening there was higher probability of detecting abnormal values;

• If Subclinical Cushing Syndrome we suggest adrenalectomy in all cases;

• We recommend complete genetic study and α-blockage before adrenalectomy on all patients with pheochromocytoma.



ABREV.: AI—Adrenal Incidentaloma; MRI— Magnetic Ressonance Imaging; SCS—Subclinical Cushing Syndrome; PHA—Primary Hyperaldosteronism; ACC—Adrenocortical carcinoma

There is no universal consensus on the pharmacological preferences among α-adrenergic blockers [18]. On recent study showed that preoperative α1-adrenoceptor antagonism with doxazosin has no benefit in maintaining intraoperative hemodynamic stability in patients with normotensive pheochromocytoma and may increase the use of vasoactive drugs and colloid infusion [19]. Another study showed the same results about symptomatic pheochromocytoma [20]. Other authors proved phenoxybenzamine, which is a nonselective α-1 and α-2 receptor blocker, provided superior intraoperative stability compared to prazosin or doxazosin [21]. Also, in contrast to phenoxybenzamine, prazosin has a short elimination half-life (2-3 hours); therefore prazosin blood concentrations may decrease to ineffective levels at the time of surgery [22]. Doxazosin elimination half-life reaches 22 hours but as it was mentioned, intraoperative hemodynamic control is weak, even though the intraoperative hypertensive crises were of short duration and were not associated with major cardiovascular complications on the study mentioned [18]. In our case report the intraoperative hypertensive crises were refractory to triple pharmacological therapy (esmolol, Isosorbidedinitrate and sodium nitroprusside) and resulted on postoperative myocardial ischemia. This conclusions show that phenoxybenzamine, being an irreversible, long-acting, nonspecific alpha-adrenergic blocking agent, is still the preferred drug for preoperative preparation to control blood pressure during perioperative period. The advantages include easy titration of the dose, less expensive, and lower incidence of reflex tachycardia, and post-operative hypotension. Therefore, for patients with normotensive pheochromocytoma that do not fulfill Roizen Criteria, an option for preoperative treatment is to use a low-dose alpha-blocker only [23] (based on current literature we suggest phenoxybenzamineinitial dose 0,1-0,2 mg/kg once or twice a day 10-14 days, as judged by the time needed to implement orthostatic hypotension 80/45 mmHg on asymptomatic patients [16,24]). Increased postoperative somnolence, headache, and postural hypotension are some of the major side effects of phenoxybenzamine. The intraoperative α-2 receptor blockade by phentolamine is hardly required in these patients.

The patient presentation reported in this case can serve as template for the scheme of management of patients with adrenal incidentalomas. He was incidentally found to have adrenal mass and was asymptomatic with near normal biochemical and hormonal studies; his age is typical for the presentation of adrenal mass. Patient was consideredpre-diabetic which is present in one in three patients with pheochromocytoma and is a clinical clue for this disease [25]. Intraoperatively he developed hyperglycemia and needed insulin infusion to control it and this could be part of stress response and glycogenolysis or due to release of cortisol hormones from the mass during manipulation.

A recent study [26] revealed that clinically silent pheochromocytomas are more prevalent than previously reported. With an adequate pre-surgical diagnosis and patient preparation [25,27,28], the prognosis of silent tumors is usually excellent.

Conclusion

It is mandatory that the anesthesiologist, as well as the urologist and endocrinologist, reach an understanding of the nature and pathophysiology of the adrenal incidentalomas and be incorporated in taking the decisions as how best to manage such patients and tailored the plan according to the patient's situation.

Based upon ours and reported experience we recommend that every asymptomatic patient with adrenal mass and biochemical evaluation suggestive of pheochromocytoma should be preoperatively submitted to alpha-antagonism to avoid potentially life threatening hemodynamic fluctuations on intraoperative and postoperative period.

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