Incidental adrenal pheochromocytoma – a report on three cases

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Sri Lanka Journal of Diabetes, Endocrinology and Metabolism 2013; **3**: 29-34

Abstract

Incidentally detected adrenal tumours pose a diagnostic challenge to the physician. Although hormonal evaluation is prioritized, it is essential to have a thorough radiological assessment of the tumour properties prior to planning the definitive management.

The aim is to report on our experience of 3 patients with an Incidental Adrenal Lesion (IAL) who were found to be hormonally 'normal' but suspicious features on CT imaging lead to surgery, after which histology revealed features of pheochromocytoma with no evidence of metastasis. Peri-operatively all three experienced haemodynamic instability.

The discussion in this article mainly emphasizes the importance of CT imaging of adrenals. It also focuses on the histopathological difficulties in predicting the tumour behavior especially in the absence of metastatic deposits.

Key words: pheochromocytoma, adrenal incidentaloma

Introduction

Incidental adrenal lesion (IAL), or incidentaloma, is an adrenal mass, which is detected radiologically when investigated for another cause. They are seen in approximately 4%-6% of the imaged population. In the evaluation it is crucial to assess the functional nature and the malignant potential of the lesion. Computed tomography (CT) imaging is the most useful in differentiating between malignant and benign masses in the evaluation of IAL. However, definitive diagnosis or exclusion of malignancy is not always possible with CT imaging alone and requires histological correlation.

Pheochromocytoma is an uncommon tumoral disease that originates from chromaffin cells in the adrenal gland. These tumours are of great clinical importance because of the catecholamines they secrete: namely, epinephrine, norepinephrine, dopamine and other vasoactive peptides. Most pheochromocytomas are benign and are a frequent cause of IAL, accounting for 1.5-23% of these masses (1,2). If the diagnosis of a pheochromocytoma is overlooked, the consequences can be disastrous, even fatal. Even if the patients are not overtly symptomatic there can be devastating complications during stressful events such as surgery.

Here we report 3 cases of asymptomatic pheochromocytoma which were detected by a systematic multidisciplinary evaluatory process.

Case reports

Case 1

Mrs. M, a 62 year old patient with diabetes mellitus (6 months) and hypertension (8 years) was investigated for recent onset non-specific abdominal pain. Her colonoscopy, upper GI endoscopy and tumour markers were all normal. The CT scan of abdomen revealed a 4.9 × 3.2 cm well defined oval shaped mass in the right suprarenal gland with central cystic area and curvilinear calcification (Figure 1).

Clinically and biochemically there were no features of endocrine over activity except for the marginally elevated ARR (aldosterone to renin ratio) of 29.61 ng/ml per ng/ml/hr. (plasma aldosterone was 25.17ng/ml and plasma renin activity 0.85 ng/ml/hr). Her 24 hour urinary VMA level was 3 µg/24 hours (normal 1-11µ/24 hours), 24 hour urinary metanephrines was 22.9 µg/24 hours (normal 25- 312 µg/24 hours) and serum testosterone was 0.3 ng/ml. Low dose dexamethasone suppression test (LDDST) revealed a suppressed serum cortisol level of 16.4 nmol/l (normal < than 50 nmol/l).

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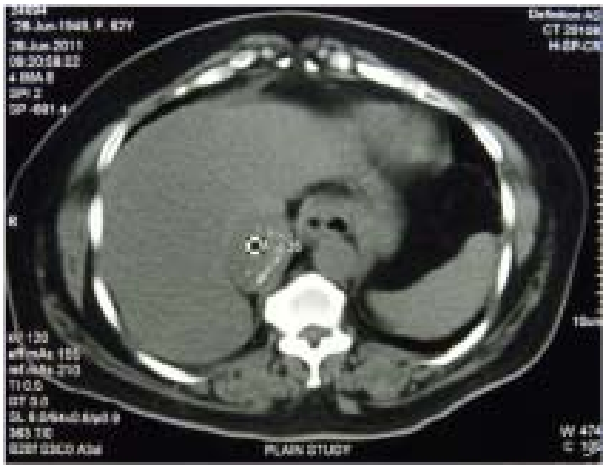

Figure 1. Unenhanced CT showing mass in the right suprarenal gland with central cystic area and curvilinear calcification.

As the initial CT scan was suspicious, the study was repeated after 5 months. This revealed a larger (4.9 × 7.2 cm) ill defined oval shaped mass with a central cystic area in the right suprarenal gland. Washout studies revealed pre-contrast attenuation of 43 HU with contrast enhancement to 127 HU and retention of contrast in the delayed phase at 112 HU. The absolute percentage washout (APW) was < 60%. As the malignant potential was high she underwent surgery during which she experienced blood pressure fluctuations and ECG changes, necessitating the use of intravenous vasodilator and fluid therapy. The maximum blood pressure recorded was 220/120 mmHg. Her post-operative period in the ICU with haemodynamic monitoring was uneventful.

Macroscopically (Figure 2) the tumour was 5.8 × 4.3 × 3.2 cm in size, exhibiting a variegated appearance with a large central necrotic area with focal areas of haemorrhage. There was no extra-adrenal extension of the tumour. A single lymph node adjacent to the tumour showed reactive hyperplasia. Microscopically the tumour was hypercellular with large bizarre nuclei and mitotic activity of 3/50 HPF including abnormal mitotic figures. The capsule was breached and tumour cells extended to the inked margin but there was no vascular or sinusoidal invasion. Immuno-histochemistry confirmed a pheochromocytoma by strong cytoplasmic positivity for Chromogranin and focal nuclear positivity for S100. Tumour cells were negative for alpha inhibin. Ki67 proliferative index was 30%. Pheochromocytoma adrenal scaled (PASS) score was more than 4. These were taken as indicators of high malignant potential and the patient was referred for chemotherapy.

There were no family members with a history suggestive of pheochromocytoma or multiple endocrine neoplasia type 2 (MEN-2) syndromes. Postoperative imaging after 3 months revealed multiple metastatic lesions in the spine and pelvis, which confirmed metastatic pheochromocytoma. Ideally an I^{123} MIBG scan should have been done but was not considered due to non-availability.

Case 2

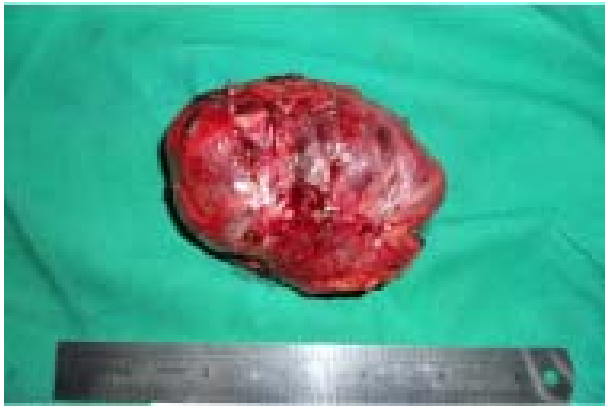

Figure 2. Macroscopic appearance of the tumour.

Mrs. S, a 46 year old patient was found to have a right IAL when she was investigated for lower abdominal pain. The main finding on imaging was an enlarged non malignant fibroid uterus which was surgically removed. Post operatively she developed hypotension which necessitated fluid resuscitation. She was then referred for endocrinology evaluation by the gynaecology team.

The CT scan revealed a well defined soft tissue mass (4.2 × 3.8 × 2.8 cm) in the right suprarenal gland having a pre-contrast attenuation of 55 HU with a low density centre. No calcifications were noted and washout studies revealed contrast enhancement to 92 HU and retention of contrast in the delayed phase at 62 HU (APW > 60%).

There was no family history of endocrine tumours. She had no symptoms or signs suggestive of endocrine over-activity and she had normal electrolytes, creatinine, fasting blood sugar and inflammatory markers. Hormonal assays revealed a suppressed serum cortisol of 18 nmol/l (<50 nmol/l) after low dose dexamethasone, a 24 hour urinary VMA level of 5.5µg/24 hours (normal 1-11µg/24 hours), 24 hour urinary metanephrine level of 189 µg/24 hours (25- 312µg/24 hours) and serum testosterone of 0.22 ng/ml.

Patient underwent enucleation of the right adrenal tumour as the lesion was radiologically 'indeterminate'. In the perioperative period although there were no spells of hypertension she developed prolonged hypotension which necessitated the use of intravenous fluid therapy.

Macroscopically the specimen was a solid tumour with central necrosis. Microscopic sections revealed

features which were compatible with pheochromocytoma of the adrenal gland with capsular and peri-adrenal adipose tissue invasion (potentially malignant biologic behaviour). The cells also had mild to moderate nuclear pleomorphism and prominent eosinophillic macronucleoli. Mitoses were rare and no atypical mitoses or necroses were seen. There was no vascular invasion but areas of compressed cortical tissue were seen to be infiltrated by the tumour. The tumour cells showed strong immuno-reactivity for chromogranin, and weak immunoreactivity for synaptophycin. The S100 protein immunoreactivity was inconclusive. The immune marker ki67 was 1.8%. PASS was less than 4.

As it was concluded that the tumour was of benign nature, the patient did not undergo any adjuvant therapy. Postoperative follow up imaging after 6 months did not reveal any evidence of local or distant metastases.

Case 3

Ms. D, a 37 year old presented with acute pyelonephritis (fever, left sided abdominal pain and vomiting) for which she was treated and subsequently investigated by ultrasound scan of abdomen which suggested a left renal mass. Further investigation by CT-IVU revealed a neoplasm (5.8 × 5.8 cm) in the region of the upper pole of the left kidney. As it was uncertain whether it was renal or adrenal in origin, endocrinological evaluation was done pre-operatively which revealed a normal biochemical and hormonal profile. Her 24 hour urinary VMA level was 4.5µg/24 hours (1-11 µg/24 hours) and the 24 hour urinary metanephrines was 105 µg/24 hours (25- 312µg/24 hours). The serum testosterone was 0.54 ng/ml. LDDST revealed a suppressed serum cortisol level of 15.2 nmol/l (less than <50 nmol/l).

She underwent exploratory laparotomy and a vascular tumour involving the left adrenal gland was removed. The kidney and regional vessels were not involved. During surgery she initially developed severe hypertension (maximum blood pressure 250/180Hgmm) with tachycardia necessitating the use of intravenous vasodilators and later developed prolonged hypotension which needed fluid, inotropes as well as ICU care with haemodynamic monitoring.

Histology revealed features compatible with pheochromocytoma of the adrenal gland, with no vascular or capsular invasion. Pheochromocytoma adrenal scaled (PASS) score was less than 4. There was no family history suggestive of either pheochromocytoma or MEN-2 syndrome.

Post-operatively she did not receive adjuvant therapy and she remained asymptomatic with no clinical or radiological features of recurrence.

Discussion

With the advancement of radiological facilities, clinicians are faced with IAL more and more. Current guidelines highlight that all patients should undergo hormonal assessment for hypercortisolism and pheochromocytoma, and those with hypertension be assessed for primary hyperaldosteronism (1, 2).

But in a poor resource setting such as Sri Lanka where relevant standard hormonal assays may not be freely available, it is very challenging to manage these cases.

In this brief report, all three patients with histologically proven pheochromocytoma underwent surgical removal of the tumours because they were radiologically 'indeterminate'. But all three patients developed perioperative hemodynamic instability despite having no features of pheochromocytoma clinically or biochemically in the pre-operative assessment. This may be due to the neoplasms being detected in the pre-biochemical (pre-secretory) phase or may be due to the low sensitivity of the available tests.

CT imaging is vital in the assessment of IAL. But in order to predict the malignant potential, it is crucial to follow the standard adrenal imaging protocols incooperating perfusion imaging. The CT criteria for predicting malignant tendency of IALs are based on their size, X-ray attenuation values on an unenhanced CT scan and contrast avidity (Figure 3). Malignancy is an uncommon cause of IAL and is suggested by tumour size of > 4 cm and attenuation values of >10 Hounsfield Units (HU). In an IAL larger than 4 cm, the chance of malignancy increases to approximately 70% (85% if larger than 6 cm) and any adrenal lesion that increases in size on serial images (usually obtained 6 months apart) can be considered malignant. The most reliable imaging method in differentiating lipid poor adenoma from an indeterminate IAL is the perfusion imaging which is based on the principle that malignant vessels have an increased capillary permeability leading to prolonged retention of contrast material within the tumour tissues. Attenuation values of the tumour are obtained in pre contrast, 60 seconds and 15 minutes post contrast images. Thus an 'indeterminate' mass has APW less than 60% (sensitivity 96%, specificity 100%) (3-5) (Table 1).

The typical imaging phenotype of a pheochromocytoma is a dense (>20 HU) and vascular mass with slow contrast washout (APW <50%). Interestingly, these characteristics are similar to radiologically 'indeterminate' lesions. They may also display haemorrhagic, cystic, and calcific changes (3, 5, 6, 7).

Our cases also highlight the difficulties of assessing the malignant potential of pheochromocytomas by

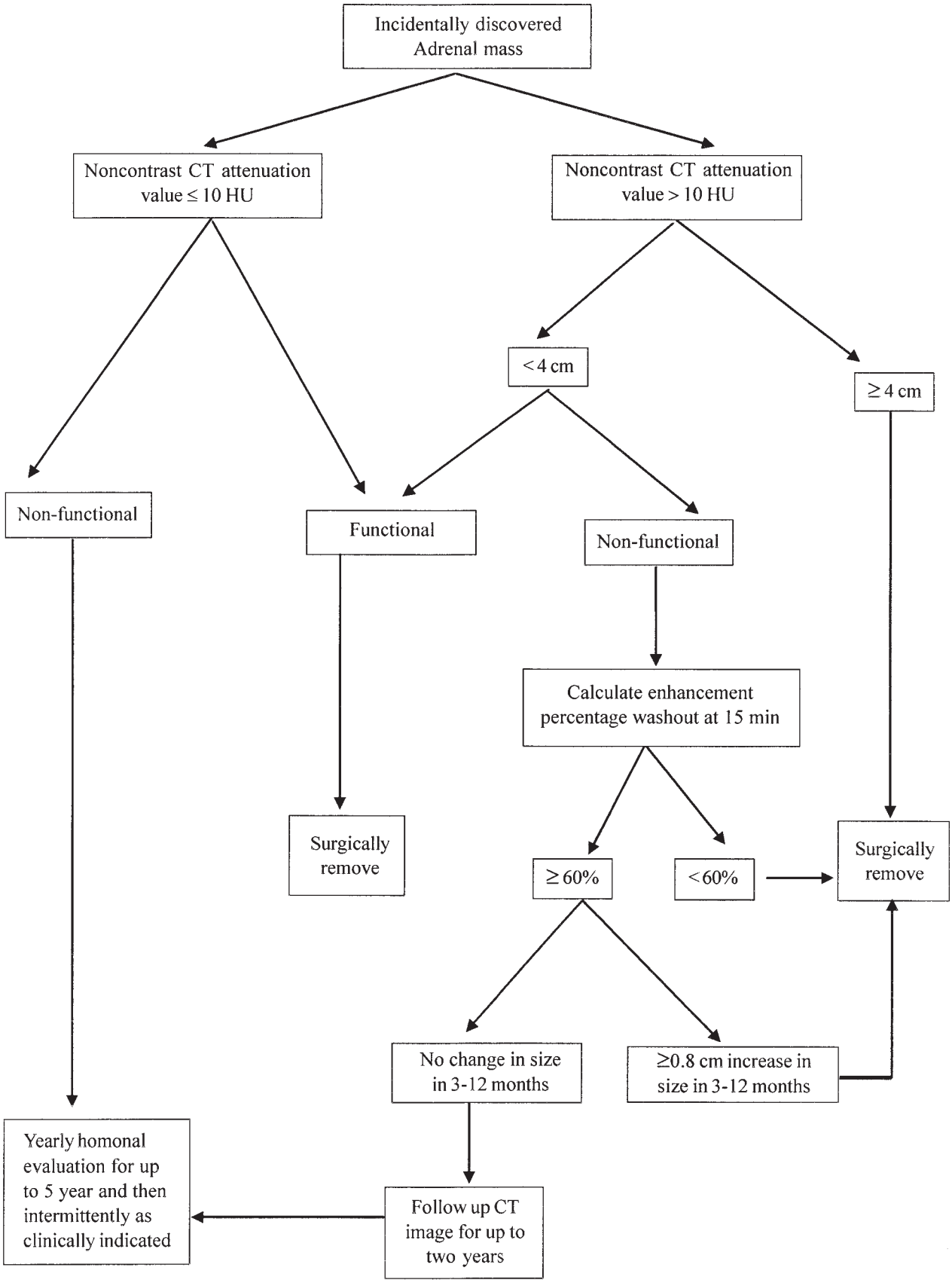

Figure 3. Algorithm depicting the recommended evaluation and treatment of patients with an IAL(2).

Table 1. Adrenal characterization on CT (4)

Exam type	*Criteria for adrenal adenoma*	*Calculation*	*Pathologic basis*
Unenhanced CT	HU ≤10	ROI in adrenal	Lipid content
Unenhanced, Dynamic, 15 min delayed	Absolute Washout ≥60%	(HU dynamic – HU delay) / (HU dynamic – HU unenhanced) × 100	Perfusion and washout
Dynamic and 15 min delayed (no unenhanced CT)	Relative washout ≥40%	(HU dynamic – HU delay) × 100 / (HU dynamic)	Perfusion and washout
Dynamic CT (No unenhanced/ delayed CT)	≥10% pixels ≤0HU	ROI then pixel histogram	Lipid content

Mayo-Smith WW. CT Characterization of Adrenal Masses. *Radiology* 2003; **226**(1): 289-90.

histological means alone. Although all 3 cases exhibited some features favouring malignancy, none displayed unequivocal pathological evidence of malignancy by accepted pathological criteria. The 2004 WHO criteria define malignancy by the presence of metastases, not local invasion. Even extensive local invasion-although potentially lethal – is a poor predictor of metastases, and a lack of apparent invasion does not preclude the development of metastases. Unfortunately there are no definitive histological or cytological criteria of malignancy (8-10).

Many attempts have been made to find markers that would predict the future behaviour of a non-metastatic pheochromocytoma; these markers include inmunohistochemical markers for growth capacity, angiogenesis and invasion markers (increased expression of Ki-67, p-53, VEGF), different catecholamine values, necrosis, vascular and capsular invasion. Some evidence suggests that multifactorial analyses can help to identify tumours with a significant risk of metastasis. Several scoring systems derived from invasion, histological growth patterns, cytological features, mitotic activity, and other characteristics have been proposed (8-10). One such scoring system is the pheochromocytoma adrenal scaled score (PASS), designed by Thompson in 2002 to determine the prognosis of pheochromocytoma based on certain histological features which are more frequently demonstrated in malignant pheochromocytomas than in benign tumours (11). A PASS weighted for these specific histological features can be used to separate tumours with a potential for a biologically aggressive behaviour (PASS score of 4 and above) from tumours that behave in a benign fashion (PASS less than 4). Patients with a PASS score of 4 and above should be followed closely for recurrence. Even though at present there is limited acceptance on PASS score, it is evident from the above three cases that it may help to decide the management of the patient. Application of these criteria to a large cohort of cases may help to elucidate the accuracy of this grading system in clinical practice (11, 12).

Staining for the proliferation marker Ki-67(MIB-1), is most consistently correlated to malignancy and is incorporated into the most recently proposed scoring system; however, studies of MIB-1 labelling lack methodological consistency. Some surveys have supported the utility of Ki-67 in assessing malignancy with thresholds for malignancy at mean labelling indices above 2% (8). In Case 1, the tumour exhibited a high Ki-67 value of 30% with a PASS score of >4 which indicated its malignant behaviour. Later the pheochromocytoma was confirmed as being malignant when she developed distant metastases. Cases 2 and 3 both had Ki-67 values less than 2% with a PASS score less than 4 which supported a benign course in future. Although they are not universally accepted, undoubtedly they helped in deciding the post-operative management of these 2 patients.

There may be a place for the use of molecular markers in future. DNA aneuploidy and tetraploidy have been considered to suggest aggressive behaviour in pheochromocytoma, but can also be found in benign tumours (12,

13). Inhibin/activin β-subunit that is expressed in the normal adrenal medulla has been found to be high in benign pheochromocytomas and near negative in malignant tumours. None of these markers is specific for the disease, and it is probably better to rely on a combination of immuno-histochemical and molecular markers for a sound earlier diagnosis. There may also be a place for genetic studies in predicting the risk of recurrence. Germ line mutations in six genes have been associated with familial pheochromocytoma, namely, the von Hippel-Lindau gene *(VHL)*, which causes von Hippel-Lindau *(VHL)* syndrome, the RET gene, leading to multiple endocrine neoplasia type 2 (MEN-2), the neurofibromatosis type 1 gene *(NF1)*, associated with neurofibromatosis type 1 *(NF1)* disease, and the genes encoding subunits B and D (and also rarely C) of mitochondrial succinate dehydrogenase *(SDHB*, *SDHD*, and *SDHC)*, which are associated with familial paraganglioma/pheochromocytoma (14).

Conclusion

This brief report aims to illustrate the diagnostic and management issues when faced with IALs which are silent pheochromocytomas. Management of these lesions is especially difficult in a poor resource setup due to the lack of access to hormonal tests, drugs and intensive care facilities and may lead to devastating complications. Here all three patients developed peri-operative haemodynamic instability despite having no clinical or biochemical evidence of hormonal activity. Thus it may be prudent that precautions be taken in all patients undergoing surgery for IAL, to minimize perioperative mortality and morbidity. These precautions may include pre-op vasodilator therapy and performing the surgeries at centres with intravenous vasodilator therapy, haemodynamic monitoring and ICU facilities.

These three cases also highlight the importance of having a multidisciplinary approach with adherence to radiological protocols with perfusion imaging, even in a poor resource setting. As there are overlapping radiological features between 'indeterminate' IALs and pheochromocytomas, the standard radiological protocol to differentiate malignant from benign lesions might lead to detection of subclinical pheochromocytomas.

Non-availability of MIBG, FDG-PET and genetic studies in our setting makes it very hard to make management decision in patients with histologically proven pheochromocytoma, especially in the absence of metastases. The lack of a well defined and accepted criterion for the histological characterization of malignant potential of pheochromocytomas makes matters worse. Multiple immuno-histochemical and molecular markers as well as scoring systems have been studied but there is currently no consensus on their role in the diagnosis of malignant potential. But it is clearly evident from the above three cases that at least until adoption of a formal scoring system, Ki- 67 marker and scoring system such as PASS may help in the management of patients with pheochromocytoma.

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