ADRENAL INCIDENTALOMAS – A MANAGEMENT APPROACH

Dr Tan Khai Tong

SUMMARY

The adrenal incidentaloma is an increasingly common clinical problem. Although most of these masses are innocuous, functioning tumours and malignancies may present as incidentalomas and potentially require surgical excision. The management approach requires an initial assessment of whether there is a functioning adrenal lesion. Functioning tumours are then subject to surgical excision. Non-functioning adrenal masses of diameter 4 cm and above may also be subject to surgery on the basis of a higher chance of malignancy. Other adrenal lesions can be observed and followed-up. There is no prefect approach to this clinical problem and each case must be evaluated on its own merit.

Key Words: Adrenal, Incidental tumours, Incidentalomas

INTRODUCTION

An adrenal incidentaloma is an adrenal mass that is discovered incidentally in the course of radiological investigation ordered or performed for conditions unrelated to the adrenal gland. This is now an increasing clinical problem as radiological tests are ordered more frequently and not uncommonly at the urging of the patients, who commonly hold the view that more tests give more conclusive evidence of the absence of ill health. In this instance, more tests can lead to more uncertainties.

The incidence of adrenal incidentalomas has been quoted as between 1% to 5%[1]. The frequency of finding an adrenal incidentaloma appears to increase with age. Over the years, as the quality of CT Scanners improve, and as more tests are ordered for an aging population, it is expected that the actual frequency will tend to towards the higher end of the above estimate – that is nearer 5% rather than 1%

The management approach to this increasingly frequent problem requires a juggling act – trying not to miss important pathology, trying not to subject the patient to unnecessary procedures or surgery and yet giving the patient sufficient answers and assurance that would allay their anxiety about discovering an incidental mass. There is obviously no perfect answer. I present here a personal management approach.

CONSIDERATIONS IN THE APPROACH TO ADRENAL INCIDENTALOMAS

There are a number of issues that need to be considered in an adrenal mass. The differential diagnosis of adrenal incidentalomas is listed in Table 1. There are two important groups. One is the group of adrenal tumours that are functioning – that is, they secrete hormone in excess and by this function could cause clinical problems. The other important group, though much less common, is the adrenal mass that represents malignancy – either primary or secondary.

Is the adrenal incidentaloma a functioning tumour?

The majority of adrenal incidentalomas are neither functioning tumours nor malignant tumours, comprising between 70% to 94% of incidentalomas discovered.[2] The malignant adrenal mass may or may not secrete hormones. The majority do not. In any case, in most instances, the discovery of hypersecretion of hormones would lead one to recommend surgical excision of the adrenal tumour. The three main hormone-producing adrenal tumours to exclude are Cortisol producing adenomas, aldosterone secreting adenomas and pheochromocytomas.

Screening for Cushing's syndrome

Of the groups of functioning tumours, the one secreting excessive Cortisol is the most frequent. There are many tests for the screening and confirmation of Cushing's Syndrome but the most useful are the overnight 1 mg Dexamethasone Suppression Test and the 24 hour Urinary Free Cortisol[3]. Both these tests can be done on an outpatient basis. If the screening tests are positive, further tests can be done, including ACTH, high dose dexamethasone suppression and other tests where indicated.

Table1

Differential Diagnosis of Unilateral Adrenal Incidentalomas

Functioning Adrenal Tumour
- Cushing's Syndrome
- Pheochromocytoma
- Primary Aldosteronism
- Adrenal Carcinoma
- Nodular Hyperplasia
- Androgen secreting tumour

Malignant Non-functioning Adrenal Tumour
- Primary Adrenal Carcinoma
- Metastatic Adrenal Carcinoma
- Other malignant tumours

Benign Non-functioning Adrenal Mass
- Adenoma
- Adrenolipoma
- Amyloidosis
- Cyst
- Ganglioneuroma
- Granuloma
- Harmatoma
- Haematoma
- Haemangioma
- Infection (eg fungal)
- Leiomyoma
- Lipoma
- Neurofibroma
- Teratoma

Pseudoadrenal Mass (mistaken as adrenal mass)
- Blood vessel
- Liver
- Lymph node
- Pancreatic mass
- Renal Mass
- Spleen
- Stomach mass

TAN KHAI TONG, Consultant Endocrinologist, The Diabetes & Endocrine Clinic

There are a number of patients who do not exhibit clear signs of Cushing's Syndrome and yet after removal of the adrenal lesion, they appear to have suppression of the pituitary adrenal axis[4]. These persons may have borderline elevation of Cortisol levels, mild degree of non-suppression of Cortisol with dexamethasone or loss of diurnal variation of Cortisol levels. The term 'Pre-Clinical Cushing's Syndrome' has been coined to describe the group of patients. There is no clear cut definition and its actual frequency may depend on the extent to which the patient is tested. The more tests that are done, the more likely that we find one or two that are abnormal. It is still unclear what percentage of patients with Pre-Clinical Cushing Syndrome eventually develop overt Cushing's Syndrome on follow-up. These patients need to be observed and repeat hormonal assessment made annually.

If Cushing's Syndrome is confirmed and the patient is sent for surgery, peri-operative glucocorticoid coverage is recommended to reduce the risk of adrenal insufficiency, circulatory collapse or even death.

Screening for pheochromocytoma

A pheochromocytoma is not a common tumour but is an important diagnosis to consider. This tumour is potentially dangerous and can lead to complications and even death in the peri-operative period, especially if the diagnosis is not suspected before surgery. Its manifestations are protean and no single test can be totally sensitive or specific[5]. Approximately 3% to 5% of adrenal incidentalomas may be pheochromocytomas. Although hypertension is common, up to 20% may be normotensive and another 30% may only have paroxysmal hypertension.

A reasonable approach would be to measure 24-hour urinary catecholamines and 24-hour urinary metanephrines in all patients with adrenal incidentalomas. It has been estimated that 99% of patients with adrenal pheochromocytoma would have an elevation of the result of one or both of these tests. Urinary vanillylmandelic acid (VMA) has lower sensitivity.

If a pheochromocytoma is suspected, peri-operative preparation is also important. Alpha and beta adrenergic blockage prior to surgery is usually recommended. The patient should also be adequately hydrated and during operation, the presence of arterial line and access to intravenous nipride would be essential.

Screening for hyperaldosteronism

The prevalence of aldosterone secreting adrenal adenoma is a subject of much debate. The classical combination of hypertension and hypokalaemia would alert one to this diagnosis and certainly if this duo is present, aldosteronism must be excluded. Virtually all patients with proven aldosteronism have hypertension[6]. The difficulty lies in trying to pick up cases which are normokalaemic. It is estimated that between 7% to 38% of cases of aldosteronism have normal potassium levels. It is rare to have aldosteronism with potassium levels above 3.9 mmol/l. Nevertheless, in the presence of hypertension, it is reasonable to screen for aldosteronism.

The two screening tests are the Plasma Aldosterone Concentration (PAC ng/dl) to Plasma Renin Activity (PRA ng/ml/hr) ratio and the 24 hour urine aldosterone. A PAC/PRA ratio of greater than 20 is a positive screening test[7].

Screening for other hormones

Sex hormone secreting tumours are very rare. Screening for these hormones is usually not necessary. In the case of the female patient, androgen-producing adenomas would lead to hirsutism. An androgen-producing tumour in a male can be difficult to detect but fortunately is very rare as well. Late onset Congenital Adrenal Hyperplasia (CAH) may present with nodularity in the adrenal gland and appear as an incidentaloma. This may be suspected from menstrual irregularity or hirsutism in the female.

Is the adrenal adenoma malignant?

This is the second important consideration in the work-up of an adrenal incidentaloma. Size had been used as an important discriminator in assessing the likelihood of malignancy. This is based on the premise that many proven adrenal carcinomas are large. The question is where to draw the line. The other possible indicators of malignancy comes from imaging and from the possible use of fine-needle biopsy. I will briefly discuss each in turn.

κ Size of the incidentaloma

For a long time, the clinical evaluation of whether an adrenal mass is likely to be malignant had centred on the assessment of its size (largest diameter) based usually on CT scan. Primary adrenocortical carcinoma is a rare tumour (estimated at between 1 per 450000 to 1 per 1.6 million annual incidence)[8]. Proven cases of adrenal carcinoma were often large and 6cm was often quoted as the threshold above which one should subject patients to surgery. Even at 6cm, benign lesions outnumber malignant ones. Copeland estimated that by using 6 cm as the criteria, benign adrenal lesions were estimated at a frequency of 1 in 4000 as compared to carcinomas estimated at 1 in 250000[9]. In one review of literature, 630 adrenal incidentalomas were operated on and 26 were found to be adrenocortical carcinomas (85% of these were ≤ 6cm)[10].

It is clear that the lower the size threshold for surgical excision, the more cases would have to be subjected to surgery in order not to miss the rare case of adrenocortical carcinoma. There are a small number of reports of adrenal carcinomas below the size of 3cm but most would agree that adrenal masses below 3 cm should not be subjected to surgery (except for functioning tumours) and should be followed up. The grey area involves those between 3cm and 6cm.

The prognosis of adrenocortical carcinoma depends to a large extent on its size at the time of surgery. Clearly if survival for adrenal carcinoma is to be improved, it must be removed while it is smaller. Furthermore, it is recognised that radiological estimation of size may often be an underestimation by 20% or more[11]. Based on these arguments, more are now advocating surgery for masses 4cm or larger and observing the rest with the view of proceeding to surgery if enlargement is subsequently demonstrated on follow-up.

Clearly this recommendation is not universally accepted but one has to draw a line somewhere. The reader is advised to read further on different views by various experts on this subject[12,13,14,15].

κ Imaging of the adrenal incidentaloma

In addition to assessing the size of the incidentaloma, imaging may give other clues regarding possible malignancy.

Plain Radiology & Ultrasound

Plain radiology has a limited role in the evaluation of adrenal incidentalomas. Calcifications can be seen in chronic granulomatous diseases like tuberculosis and histoplasmosis or a chronic hematoma. Ultrasound can differentiate between a cyst and a solid tumour. It is however inferior to CT Scan in providing precise anatomical definition.

Computerised Tomography (CT) Scan

Most cases of adrenal incidentalomas are picked up on CT Scan. Most adrenal masses more than 1 cm in diameter can be reliably detected. In most instances, CT is the modality of choice in the radiological evaluation of an adrenal incidentalomas[16]. In some instances, CT can confidently define the etiology of the lesion. These include the simple adrenal cyst, myelolipomas and hemorrhage.

A low attenuation on unenhanced CT can help to differentiate adrenal adenomas (which have lower densities) from malignant or metastatic lesions. However, the specificity of attenuation values alone has not gained clinical acceptance for discriminating between benign and malignant disease.

Magnetic resonance imaging (MRI)

MRI can also offer some information in discriminating between benign and malignant disease. It can be particularly useful if a pheochromocytoma is suspected because pheochromocytomas exhibit high signal intensity on the enhanced T2 weighted image[17].

MRI can offer good anatomical information, show extension into adjacent structures and show the relationship of the adrenal tumour and major vessels. This information may in some cases be sufficient to confidently discriminate between benign and malignant tumours.

Chemical shift imaging may differentiate adrenal adenomas, which contain abundant lipids, from non-adrenal lesions.

Radioisotope Scanning

These may be useful in specific situations. Pheochromocytoma can be detected using MIBG scan. This can be ordered if pheochromocytoma is already suspected based on biochemistry as it can help to show extra-adrenal sites of pheochromocytoma. Neuroblastomas and paragangliomas can also be imaged using MIBG scan.

Angiography

This is of limited application, eg in selected cases of aldosteronism where selective venous sampling for cortisol and aldosterone may help in localising the source of aldosteronism.

κ Fine Needle biopsy

Although fine needle biopsy has the potential of yielding a histological diagnosis without invasive surgery, there are a number of limitations. There is a risk if needle biopsy is inadvertently performed on a case of pheochromocytoma even if the lesion is cystic in appearance. Biochemical tests to rule out a pheochromocytoma is recommended before considering fine needle biopsy.

In the case of a malignant neoplasm, there is a risk of seeding the peritoneum with malignancy. There is also difficulty in differentiating some cases of adrenal cortical adenoma from adrenocortical carcinoma on fine needle biopsy. One possible application is in the case of bilateral adrenal masses, where a diagnosis of infection can be made on needle biopsy.

In the case of proven malignancy, the presence of an adrenal mass may or may not alter the line of management. If there are also other sites of metastases (proven), the management is unlikely to be altered much by the presence or absence of adrenal metastases. However, if there are no other areas of metastasis demonstrated, the presence of adrenal secondaries would alter the staging and possibly the overall mode of treatment. In this setting, there may be a place for fine needle aspiration biopsy.

Overall, it must be said that fine needle biopsy of the incidental adrenal mass has limited application.

A CLINICAL APPROACH TO THE ADRENAL INCIDENTALOMA

A clinical approach is summarised diagramatically in Figure 1. As in good clinical practice, it starts with a careful history and clinical examination. Symptoms and signs of functioning tumours are looked out for. The possibility of malignancies should be considered. In the occasional case, hypoadrenalism may be seen. The presence of MEN syndrome alerts one to the possibility of a pheochromocytoma.

Assuming that the history and clinical features are non-conclusive, the next step is to rule out a hyperscereting

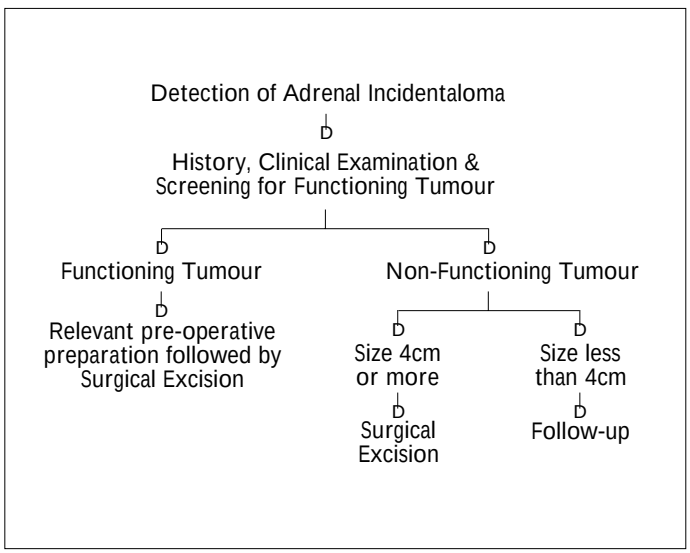

Figure 1: Approach to the Management of Adrenal Incidentaloma

adrenal tumour. Screening for Cushing's syndrome and pheochromocytoma should be considered for all. If hypertension or a history of hypertension is present, aldosteronism should be screened for as well. In the case of female patients, symptoms and signs of androgen excess would mandate screening for androgen excess as well.

If a hypersecreting adrenal adenoma is confirmed upon the screening test, further tests for each syndrome (eg Cushing's Syndrome or Pheochromocytoma) should be carried out. This is then followed by relevant pre-operative preparation and then surgical excision of the adrenal tumour.

If there is no hypersecretion of hormones, the next step is to consider if excision is warranted on the basis of possible malignancy. Although there is no clear answer with regards to size, it is still the simplest way of deciding. I would consider surgical excision for tumours 4cm in diameter and above. CT Scan and other imaging techniques may help to sway the decision in borderline cases (3cm to 6cm).

Choice of Surgical Approach

The advent of laparoscopic adrenalectomy has led to shorter hospital stays and better patient acceptance of adrenalectomy[18]. Of course the availability of experienced and competent laparoscopic surgeons is a requirement. Except for invasive malignant tumours and very large tumours (more than 10cm), most adrenal incidentalomas can now be safely removed via the laparoscopic approach.

Follow-up

Follow-up is an important part of the clinical approach to an adrenal incidentaloma. No single approach is fool-proof. Unless all cases are subject to surgery, in which most would be arguably 'unnecessary', there may be cases that are hormone-secreting or malignant tumours that are missed. On follow-up, a repeat CT scan should be done to look for any increase in size. The first follow-up should be between 3 to 6 months with another follow-up at 12 months. A repeat hormone screening after 12 months is recommended. Subsequently, annual follow-up visits are recommended.

Special Considerations

Special considerations may be given to certain patients and one may deviate from the usual approach. Patients who are poor surgical candidates may be observed and followed up instead of proceeding to surgical excision, especially if the hormone test results or the size of the tumour are in the equivocal ranges. One may lean towards surgical excision if follow-up of the patient is not possible or difficult. Patients who are extremely anxious and cannot accept any ambiguity may want to opt for surgical excision but they must be warned of the risks of surgery.

Bilateral Adrenal Incidentalomas

Occasionally the incidental adrenal tumour is bilateral. It is useful to note the possible etiologies of bilateral adrenal masses as listed in Table 2. As in the case of the unilateral adrenal mass, the approach starts with history, clinical examination and the screening of hypersecretion of hormones. One main difference is that in the case of bilateral masses, adrenal hypofunction is not uncommon. A Short Synacthen Test is still a good method of ruling out adrenal cortical hypofunction and this is important, especially if surgery is considered. The other main difference is that in some countries within South East Asia, infections (like histoplasmosis) are not uncommon causes of bilateral adrenal masses (often with hypocortisolism). Fine needle biopsy may be useful in this setting to diagnose infection of the adrenal glands.

Table2

Differential Diagnosis of Bilateral Adrenal Incidentalomas

Malignancy	Metastatic Carcinoma Lung (most common) Breast Kidney Colon Melanoma Lymphoma Others
Infection	Tuberculousis Fungal infection
Hemorrhage	
Bilateral Pheochromocytoma	
Adrenal Hyperplasia	Congenital Adrenal Hyperplasia Cushing's Disease
Amyloidosis	

CONCLUSION

This paper on the clinical approach has been brief and details have been left out in the interest of presenting only an overview of the subject. Details of each condition (Pheochromocytomas, Cushing's Syndrome, etc), its diagnosis and treatment, can be found in review articles on each of these subjects.

As we learn more about the natural history of adrenal incidentalomas, the management approach will become clearer and may change over time. It would be desirable to have more specific tests to determine its nature without the need to resort to surgery. However it is likely that there will never be one approach that can satisfy all requirements. Finally, it is the clinical judgement and the communication skills of the clinician that is equally important. Modifications to the management approach may be made for each patient depending on their age, mental attitudes, anxiety levels and so on.

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