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Clinical significance of the large adrenal mass

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Current clinical teaching indicates that large (>5 cm in diameter) adrenal masses are often malignant. In a retrospective analysis of patients studied between 1977 and 1988 with computed tomography (CT), adrenal scintigraphy, and when available, magnetic resonance imaging (MRI) 45 were found to have adrenal masses greater than 5 cm (range 5–19 cm) in diameter. Thirty were benign (16 phaeochromocytomas, six adrenocortical adenomas, four adrenal cysts, two myelolipomas, an adrenal hematoma and a ganglioneuroma). Of 15 malignant masses, there were seven adrenocortical carcinomas, five adrenal metastases and three adrenal lymphomas. With the exception of the adrenal myelolipomas, cysts, and the ganglioneuroma neither CT nor MRI demonstrated sufficient diagnostic specificity to distinguish benign from malignant lesions. Functional scintigraphy with ^{131}I-6-β-iodomethyl-19-norcholesterol for suspected adrenocortical lesions and ^{131}I-metaiodobenzylguanidine for suspected phaeochromocytomas frequently provided useful information.

The differential diagnosis and optimal management of coincidentally discovered adrenal masses remains a matter of controversy which has been heightened by the availability of high-resolution computed tomography (CT). Abnormalities of adrenal morphology – masses larger than 1 cm in diameter – are found incidentally in approximately 1 per cent of all patients undergoing abdominal CT[1–3] and up to 26 per cent of patients with primary extra-adrenal malignancies have adrenal metastases at autopsy[4]. Adrenal cortical tumours producing syndromes of steroid hormone excess have an estimated incidence of approximately 4 per million per year and are equally divided between adenomas and carcinomas[5]. Phaeochromocytomas occur with an estimated incidence of 1·5 million per year with only 10 per cent being malignant[6]. Reviews of functioning[5,7] and 'incidental'[8] adrenal masses have emphasized the positive correlation between size of the mass and the likelihood of malignancy. Recommended thresholds for surgical exploration have included diameters of 3–3·5 cm (References 1, 2 and 9), 5 cm (Reference 10) and 6 cm (Reference 8). Among 'non-hyperfunctioning', incidental, unilateral adrenal masses size was found to be a poor discriminator of malignancy, with benign masses ranging between 1 cm and 7 cm in diameter and malignant masses between 1·5 cm and 10 cm (Reference 11). In a subgroup of 28 patients with known extra-adrenal malignancies only ten such masses proved to be adrenal metastases[12]. The clinical, radiologic, scintigraphic and pathological characteristics of large adrenal masses (5 cm or greater in diameter), both hyperfunctioning and non-hyperfunctioning, referred to Ann Arbor between 1977 and 1988 have been studied.

Patients and methods

Individuals with unilateral or bilateral adrenal masses 5·0 cm in diameter or larger were identified from the database of patients referred for adrenal scintigraphy with ^{131}I-6-β-iodomethyl-19-norcholesterol (NP-59), 29 cases from a total of 468 studies (1977–1988) or ^{131}I-metaiodobenzylguanidine (MIBG), 16 cases from a total of 52 sporadic intra-adrenal phaeochromocytomas (1981–1988). Adrenal cortical and/or medulla function was evaluated in all cases with some combination of the following measurements: plasma cortisol (basal morning and evening levels, and levels following overnight suppression with oral dexamethasone and/or stimulation with intravenous adrenocorticotrophic hormone (ACTH); 24-h urinary excretion of free cortisol of 17-hydroxycorticosteroids (17-OHCS); plasma aldosterone and renin activity; 24-h urinary aldosterone excretion; plasma androgens (testosterone, androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate); 24-h urinary 17-ketosteroid (17-KS) excretion; plasma catecholamines (adrenaline and noradrenaline); and urinary catecholamine and metabolite (vanillylmandelic acid (VMA), metadrenaline and normetadrenaline) excretion.

Computed tomography was performed in 43 of 45 patients using a variety of scanners between 1977 and 1988 including EMI 5005 (EMI Limited, Middlesex, England), Picker 1200 SC (Picker International Wood Dale, Illinois, USA) GE 8800 and 9800 (General Electric Corporation, Milwaukee, Wisconsin, USA). In most instances, 10 mm contiguous sections were obtained through the region of the adrenal glands. Recently MRI was performed in ten of the 45 patients using a Diasonics MT/A (Palatine, Illinois, USA) superconducting magnet operating at 0·35 T. Generally, 10 mm thick contiguous sections were obtained using a variety of non-gated spin-echo sequences (SE 500/28-30 and SE 2000/28-30, 56-60,100)[13]. The relative intensity of each adrenal lesion was compared visually with the liver and then categorized as hypo-, iso- and hyperintense. Scintigraphy was performed with institutional review board approval and with the patients' informed consent. Thyroidal uptake of free ^{131}I-iodide was blocked with oral Lugol's solution or a saturated solution of potassium iodide (SSKI)[14]. When appropriate, adrenocorticotrophic hormone (ACTH)-dependent uptake of the NP-59 by the zona fasciculata/reticularis was suppressed by pretreatment with oral dexamethasone[15]. Scans were obtained 3–7 days after the intravenous administration of 37 MBq(1 mCi) of NP-59 (Reference 13) or 24–72 h after the intravenous administration of 18·5 MBq (0·5 mCi)/1·73 m^2 (maximum, 37 MBq (1·0 mCi)) of ^{131}I-MIBG[16]. Imaging was performed using a wide-field-of-view γ-camera fitted with a high-energy, parallel-hole collimator and interfaced to a dedicated computer. Images were obtained for 20 min or 50 000 counts per view.

The scintigraphic studies were interpreted using criteria previously described[17,18]. In all but three cases, a tissue diagnosis was made by CT-guided fine-needle biopsy, surgery or autopsy. The maximum diameter of the mass was recorded; in patients with bilateral masses, the maximum diameter of the larger mass was used for statistical purposes. Statistical analysis was by Student's *t*-test and the χ^2 test.

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Results

The 45 patients ranged in age from 22 years to 88 years (median, 53·5 years; mean(s.d.), 54·1(14·9) years). There were 24 men (median age 55·5 years, range 42–74 years) and 21 women (median age 54 years, range 22–88 years). The masses were on the right side in 23 cases, (ten men, 13 women), on the left in 16 (ten men, 6 women) and bilateral in six (four men, two women). The maximum diameter was 19 cm (median, 7·0 cm; mean(s.d.), 8·1(3·4) cm). There was no significant sex difference in the size of the masses. Five patients presented with endocrine dysfunction compatible with adrenocortocal disease, 16 with hypertension as a result of phaeochromocytoma and 24 patients were studied with CT for reasons other than suspected adrenal disease, usually abdominal pain. Of the incidentally discovered unilateral adrenal masses 23 were included in previous reports that focused on the use and efficacy of scintigraphy in the evaluation of the silent mass[11,12].

Pathology (Table 1)

The masses were proved cytologically and/or histologically to be malignant in 15 cases – primary adrenal cortical carcinoma in seven and adrenal metastases in eight – and benign in 27 cases. The remaining three patients declined biopsy or surgery, but their masses remained unchanged on follow-up of 6 months (one case) to 2 years (two cases) and demonstrated a concordant scintigraphic pattern with NP-59 (i.e., uptake of NP-59 was increased on the side of the mass[11]); they were therefore presumed to be benign, adrenocortical adenomas. Malignant masses (mean maximal diameter(s.d.) 9·7(4·0) cm) were larger than benign masses (mean maximal diameter(s.d.) 6·2(1·1) cm; $P=0·006$). Similarly, primary adrenocortical carcinomas were significantly larger (11·4(4·2) cm) than cortical adenomas (5·8(1·3) cm, $P=0·017$) or phaeochromocytomas (6·9(1·5) cm, $P=0·017$). There was no significant difference in size between primary (11·4)(4·2) cm) and metastatic (8·1(3·3) cm) malignant adrenal masses ($P=0·11$), but bilateral masses were always metastatic (large-cell bronchogenic carcinoma, two cases; squamous-cell oesophageal carcinoma, one case; diffuse histiocytic lymphoma, three cases). Nine of 38 unilateral masses were malignant. There was no sex difference between the prevalence of benign or malignant masses, or of primary or metastatic malignant masses ($P>0·4$).

Clinical features (Table 2)

Most commonly, the adrenal masses were discovered during the staging and evaluation of patients with known, non-adrenal malignancies – bronchogenic carcinoma (four cases), oesophageal carcinoma (two cases), adenocarcinoma of the colon (one case), transitional-cell carcinoma of the bladder (one case), and non-Hodgkin's lymphoma (one case). In none of these patients were the masses associated with any evidence of obvious adrenal dysfunction, and in only one case (case 1, below) was the mass suspected clinically – thus, the masses were 'incidental' in eight of these nine cases. In three of the patients, the adrenal masses were not due to metastases:

Table 1 *Pathological diagnoses*

Pathology	No. of cases	Maximum diameter (cm) Median	Range	Side
Benign:	30	6·0	5·0–8·0	17R, 13L
Cortical adenoma	6*	5·2	5·0–8·0	5R, 1L
Myelolipoma	2	6·8	6·5–7·0	1R, 1L
Cyst	4	6·0	5·0–7·0	1R, 3L
Haematoma	1	8·0	–	1R
Ganglioneuroma†	1	6·0	–	1R
Phaeochromocytoma	16	7·0	5·0–11·0	8R, 8L
Malignant:	15	9·0	5·0–19·0	6R, 3L, 6B
Cortical carcinoma	7	11·0	7·0–19·0	4R, 3L
Metastatic carcinoma	5	6·0	5·0–9·0	2R, 3B
Lymphoma	3	10·0	8·0–15·0	3B
Total	45	7·0	5·0–19·0	23R, 16L, 6B

*Tissue diagnosis not available in three cases – tumours stable on extended follow-up (see text); †Juxta-adrenal tumour; R, right; L, left; B, bilateral

Table 2 *Clinical presentation*

Known extra-adrenal malignancy*		9
Lung (large cell)	4	
Oesophagus (squamous cell)	2	
Colon (adenocarcinoma)	1	
Bladder (transitional cell)	1	
Lymphoma (diffuse histiocytic)	1	
Abdominal pain		10
Hypertension†		22
Primary aldosteronism	2	
Phaeochromocytoma	16	
Adenoma	3	
Cyst	1	
Hyperandrogenism		2
Other*		2
Anaemia, fever (lymphoma)	1	
Adrenal insufficiency (lymphoma)	1	

*CT performed for reasons other than suspected renal disease; †CT performed for suspected adrenal disease (e.g. aldosteronism, phaeochromocytoma) in 18 of the 22 cases

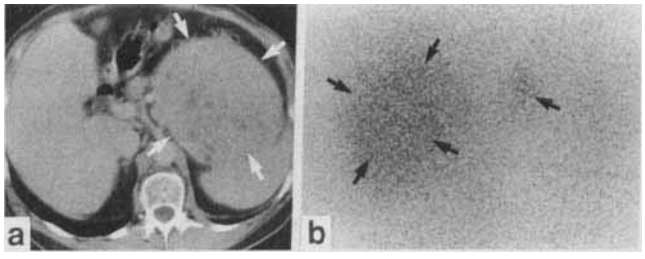

Figure 1 **a** *Abdominal computed tomography scan depicts a large left-sided retroperitoneal mass (arrows) and enlarged periaortic lymph nodes.* **b** *Posterior* ^{131}*I-6-β-iodomethyl-19-norcholesterol scan demonstrates radiotracer uptake in the mass (arrows) and in the normal right adrenal gland (arrow)*

Case 1. A 61-year-old man presented initially with dysphagia and weight loss due to a squamous-cell carcinoma of the oesophagus. A left upper quadrant abdominal mass was noted on clinical examination. A CT scan of the abdomen showed a large, retroperitoneal mass of mixed density with punctate calcifiation, associated with multiple, abnormally enlarged, retroperitoneal lymph nodes (*Figure 1*). The right adrenal gland appeared normal. An NP-59 scan showed extensive uptake on the left consistent with a functioning, but not hyperfunctioning adrenocortical tumour; however, uptake on the right was not suppressed (*Figure 1*). CT-guided fine-needle biopsy of the mass was consistent with adrenocortical carcinoma. At operation, a $19 \times 14 \times 10$ cm, 1175 g, well-differentiated, left adrenocortical carcinoma was removed. Several of the retroperitoneal lymph nodes were biopsied and found to contain metastatic squamous-cell carcinoma – there was no evidence of extra-adrenal spread of the adrenocortical tumour.

Case 2. A 67-year-old man, had a Dukes' stage C carcinoma of the colon resected in 1978. He presented 9 years later with a right abdominal wall mass, which proved to be an abscess. During the evaluation of this mass, a CT scan of the abdomen showed a mixed-density, $7·0 \times 6·5$ cm right adrenal lesion. The

mass was non-functioning on an NP-59 scan. CT-guided fine-needle biopsy yielded only a few lipid droplets, but no cellular material. At laparotomy, a 140 g right adrenal myelolipoma was removed. There was no evidence of metastatic colonic carcinoma.

Case 3. A 66-year-old man, underwent abdominal CT scanning during staging of an invasive, transitional-cell carcioma of the bladder (*Figure 2*). A 5·0 cm right adrenal mass was noted, with a morphologically normal left adrenal gland. An NP-59 scan showed a discordant pattern of imaging, i.e., tracer uptake was reduced on the side of the mass[11]. A CT-guided fine-needle biopsy was unsuccessful. A benign right haemorrhagic adrenal cyst was removed at operation.

In ten patients, the adrenal masses were discovered during the evaluation of abdominal, chest or back pain. The pain could reasonably be attributed to the mass in five of these patients – two with primary adrenocortical carcinoma, two with an adenoma where one was later shown to be autonomously functioning and one with a benign cyst. The initial investigation which disclosed the adrenal mass was plain radiography (one case), intravenous urography (three cases), abdominal ultrasonography (three cases) and CT scanning (three cases). Although none of these patients had clinical evidence of adrenal dysfunction, one (a 35-year-old woman with a 12 × 10 cm left adrenocortical carcinoma with retroperitoneal, pleural and pulmonary metastases) had mildly elevated urinary 17-KS levels (56 μmol/d (reference range: 14–49 μmol/d)) and a second patient (64-year-old man with mild hypertension and emphysema and a 6 cm right adrenal mass) (*Figure 3*) and an elevated urinary free cortisol (284·4 nmol/d (reference range: < 140 nmol/d)) and an a.m. plasma cortisol of 248·4 nmol/l (reference range: < 138 nmol/l) 12 h after 1 mg of oral dexamethasone. In five patients in whom the pain could not be attributed to the adrenal mass and where there was no evidence of adrenal cortical or medullary dysfunction, the masses could be considered 'incidental'. These were benign (adenoma, cyst, hematoma, myelolipoma, juxta-adrenal ganglioneuroma) lesions.

A total of 22 patients had adrenal masses found in the course of evaluation of hypertension. Of these 16 patients presented with episodic hypertension and headaches and in all elevated plasma and urinary catecholamines and their metabolites were noted. In each case a benign-appearing unilateral, sporadic, intra-adrenal, phaeochromocytoma was found (*Figure 4*). Two patients, who had the typical biochemical features of primary aldosteronism and in whom the masses proved to be functioning adrenocortical carcinomas, have each been the subjects of separate case reports[19,20]; their tumours measured 7 cm and 11 cm in maximal diameter and both neoplasms accumulated NP-59, despite dexamethasone suppression. An additional patient has had intermittent, mild hypokalemia but no evidence of primary aldosteroism, or other biochemical abnormality referable to adrenal cortex or medulla dysfunction. The masses in this group were initially found by intravenous urography in two cases, abdominal ultrasonography in two cases, and by CT scanning in the remaining 18 cases. Apart from the two patients with primary aldosteronism and the 16 cases of phaeochromocytoma, biochemical evaluations were normal. The remaining masses consisted of cortical adenomas (three cases) and a benign adrenal cyst.

Two women presented with symptoms of hyperandrogenism:

Case 4. A 22-year-old woman, presented with hirsutism, secondary amenorrhea, acne and increased libido. Plasma total testosterone (9·5 nmol/l (reference range: 0·84–2·31 nmol/l)) and DHEA sulphate (15·5 μmol/l (reference range: 2·2–7·3 μmol/l)) and urinary 17-KS levels (197·4 μmol/d) were elevated. Urinary free cortisol and 17-OHCS excretion were normal and plasma cortisol suppressed normally following dexamethasone administration. An abdominal CT scan showed

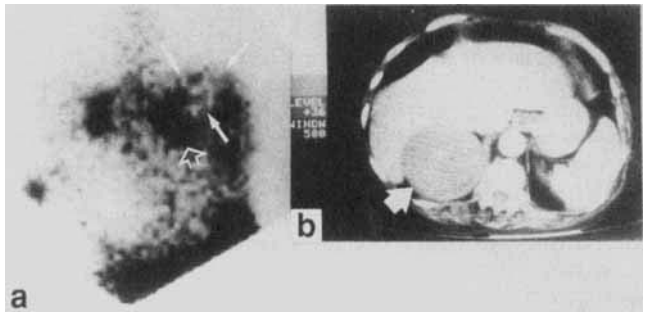

Figure 2 **a** *Posterior ^{131}I-6-β-iodomethyl-19-norcholesterol scintiscan depicts a normal left adrenal, a medially displaced right adrenal and a 'cold' area located laterally to the right adrenal (arrow).* **b** *Abdominal computed tomography scan identifies a 5 cm homogenous mass with a calcified rim in the right adrenal area (arrow)*

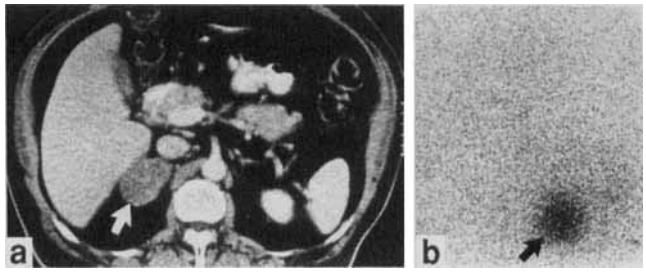

Figure 3 **a** *Abdominal computed tomography scan identified a large (6 cm) right adrenal mass (arrow).* **b** *Posterior chest and upper abdominal ^{131}I-6-β-iodomethyl-19-norcholesterol scintiscan depicts a solitary focus of radiotracer uptake that corresponds to a Cushing's adenoma. The contralateral adrenal is not visualized due to suppression of adrenocorticotrophic hormone and ^{131}I-6-β-iodomethyl-19-norcholesterol uptake into the normal adrenal*

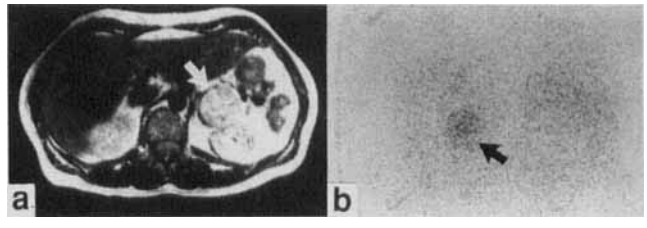

Figure 4 **a** *T2 weighted abdominal magnetic resonance imaging scan of the abdomen of a 67-year-old man with episodic hypertension and elevated plasma catecholamines (E-2019 pmol/l, reference range 0–545 pmol/l, NE-6·86 nmol/l, reference range 0–4·5 noml/l, urinary metenphrine-23·4 μmol/d, reference range < 4·63 μmol/d, vanillylmandelic acid 53·9 μmol/d, reference range < 35 μmol/d) and a 5 cm left adrenal phaeochromocytoma (arrow).* **b** *^{131}I-metaiodobenzylguanidine scintiscan depicts the neoplasm as a solitary focus of ^{131}I uptake in the left abdomen*

a large, partially calcified, right adrenal tumour extending into the inferior vena cava. The affected adrenal could not be visualized with NP-59, while uptake by the left adrenal was normal, a not unexpected circumstance since cortisol and its metabolites were normal. At operation, the tumour was found to extend to the right atrium; a 14 × 13 × 8 cm, 815 g primary adrenal cortical carcinoma was removed via a combined thoracoabdominal approach with cardiopulmonary bypass.

Case 5. A 27-year-old woman, presented because of secondary amenorrhea and obesity. She was noted to be mildly hypertensive but had no other clinical stigmata of Cushing's syndrome. Abdominopelvic ultrasonography demonstrated a left adrenal mass, approximately 6·5 cm in diameter. Biochemical evaluation showed elevation of plasma total (5·04 nmol/l (reference range: 0·88–3·33 nmol/l)) and free testosterone (0·98 nmol/l (reference range: 0·11–0·46 nmol/l)),

plasma DHEA sulphate (21·2 μmol/l (reference range: 0·84–8·24 μmol/l)), and increased urinary 17-KS excretion (74·9 μmol/d) which failed to suppress (85·1 μmol/d) after high-dose oral dexamethasone. In addition, although plasma cortisol levels and urinary free cortisol and 17-OHCS excretion were normal, there was loss of the normal diurnal variation in plasma cortisol, and urinary free cortisol excretion failed to suppress normally after dexamethasone. A CT scan confirmed a large left adrenal mass with no evidence of extra-adrenal extension (*Figure 5*). An NP-59 scan failed to demonstrate radiopharmaceutical uptake in either adrenal, an expected consequence of autonomous glucocorticoid excess from an adrenocortical carcinoma with suppression of ACTH and contralateral radiotracer accumulation[21] (*Figure 5*). A 7 × 6 × 5 cm, 105 g, primary adrenocortical carcinoma was resected; the patient required glucocorticoid support in the early postoperative period.

The remaining two patients had lymphomas involving the adrenals. A third patient with adrenal involvement by lymphoma has been mentioned among the patients with known extra-adrenal primary malignancies (above):

Case 6. A 53-year-old woman was evaluated in 1982 after treatment for stage IVb diffuse histiocytic lymphoma. In 1986, she presented once again in relapse with clinically bulky abdominal disease. Abdominal CT and MRI scans demonstrated very large, bilateral adrenal masses (maximum diameter 15 cm) where the largest mass (right) was hyperintense and the smaller, (left) was hypointense as compared with liver on a T-2 weighted MRI scan (*Figure 6*). An NP-59 scan demonstrated a small focus of residual cortical activity on the right and no evidence of adrenocortical function on the left (*Figure 6*). CT-guided fine-needle biopsy of the left adrenal mass confirmed lymphomatous involvement. Biochemical evaluation showed no evidence of adrenocortical hormone excess; she had no clinical evidence of glucocorticoid deficiency.

Case 7. A 57-year-old woman, had been extensively investigated for a longstanding anemia and neutropenia. In 1977, she developed fever and weight loss. An ultrasound examination of her abdomen showed a rounded mass below the right lobe of the liver. An abdominal ^{67}gallium citrate scan showed bilateral adrenal uptake of ^{67}gallium citrate, but both adrenals failed to accumulate NP-59[22]. There was no evidence of adrenocortical hypofunction but the possibility of glucocorticoid insufficiency was not formally evaluated. At laparotomy, the patient was found to have diffuse histiocytic lymphoma involving the right adrenal, with widespread retroperitoneal disease. Postoperatively, she suffered recurrent fevers, despite empiric antibiotic therapy, recurrent supraventricular tachyarrhythmias and episodic hypotension, and died approximately 1 week after surgery. At autopsy, widespread retroperitoneal lymphoma was confirmed; the right adrenal (which had been biopsied) measured 7 × 4 × 2 cm and was partially haemorrhagic, and the left measured 8 × 6 × 6 cm. There was no identifiable residual adrenal tissue.

Case 8: A 59-year-old man who had been treated for diffuse histiocytic lymphoma in 1984 and was considered to be in remission. In mid-1986 he presented with fever and muscle weakness. There was no evidence of recurrent lymphoma on clinical examination, but he was noted to be deeply tanned and hypotensive. Initial plasma biochemistry was as follows: sodium 131 mmol/l, potassium 8·2 mmol/l, bicarbonate 16 mmol/l, creatinine 371·3 μmol/l and calcium 3·38 μmol/l. Adrenal insufficiency was diagnosed and confirmed by finding subnormal plasma cortisol levels which failed to rise after the administration of ACTH. Appropriate hormone replacement therapy was commenced. A CT scan was not performed on that occasion. He presented again 3 months later with abdominal pain. A CT scan showed bilateral adrenal enlargement (7 cm diameter on the right, 10 cm on the left) as well as multiple intra-abdominal and retroperitoneal lymph nodes and pancreatic enlargement. An NP-59 scan demonstrated bilateral adrenal absence of iodocholesterol uptake. Combination chemotherapy was recommended, but 1 month later the patient developed cerebral lymphoma with leukoencephalopathy.

Prediction of pathology from imaging studies

In 12 of the 15 patients with primary or metastatic adrenal malignancies, one or more of the following features were evident on the imaging studies: associated lymphadenopathy, invasion of the inferior vena cava, bilateral adrenal masses, hepatic or pulmonary metastases, a 'discordant' pattern of imaging between the CT and NP-59 scan[11], and bilateral non-visualization of the adrenals on the NP-59 scan[11]. Retroperitoneal lymph node enlargement and/or discordant imaging were also present in five of the 13 patients with benign lesions (truly non-functioning and space occupying, e.g. cyst and myelolipoma, masses)[11]. An additional patient had a normal pattern of NP-59 scintigraphy despite the presence of a 6·0 × 5·5 cm mass on the right; she proved to have a juxta-adrenal ganglioneuroma with a normal right adrenal gland. The uptake of iodocholesterol was seen in the adrenal mass of four patients with well differentiated adrenocortical

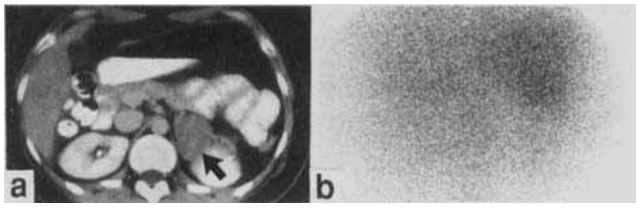

Figure 5 **a** *Abdominal computed tomography scan identifies a 7 cm left adrenal mass (arrow).* **b** *Posterior ^{131}I-6-β-iodomethyl-19-norcholesterol scan depicts no discernible adrenal uptake in a patient with a primarily androgen-secreting adrenocortical carcinoma*

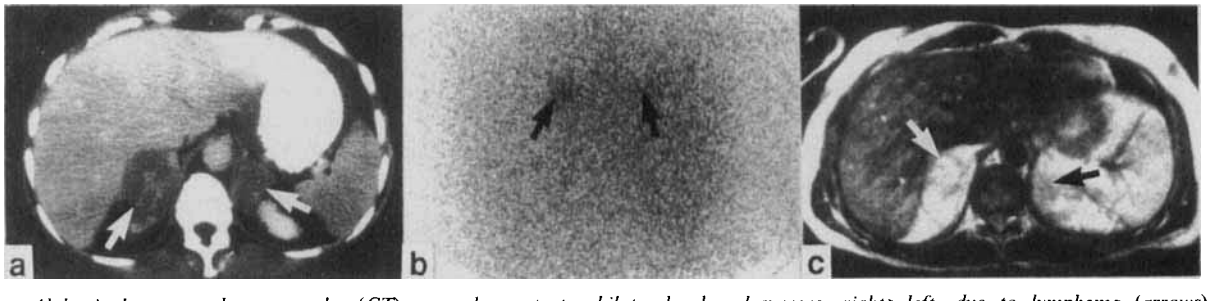

Figure 6 **a** *Abdominal computed tomography (CT) scan demonstrates bilateral adrenal masses, right > left, due to lymphoma (arrows).* **b** *^{131}I-6-β-iodomethyl-19-norcholesterol scan depicts the adrenal involvement with discernible radiotracer uptake on the left and faint uptake on the right (note the discordance with the CT scan).* **c** *T2 weighted abdominal magnetic resonance imaging (MRI) scan (at the same level as the CT scan) demonstrates the right mass (arrow) as hyperintense and the left (arrow) as more isointense as compared with the MRI signal of the liver*

carcinomas; two with glucocorticoid and two with mineralocorticoid excess. In 16 patients with intra-adrenal, sporadic, non-familial, phaeochromocytomas, ^{131}I-mIBG scintigraphy was successful in identifying all but one case. Magnetic resonance imaging was performed in eight of the cases and successfully identified the abnormal anatomy in all of these cases. CT-guided fine-needle biopsies were performed in 13 patients. Three biopsies were non-diagnostic and no complications of needle biopsy were noted.

Discussion

In this series, patients with large adrenal masses were twice (30/15) as likely to have benign as malignant masses. If only patients with masses larger than 6 cm diameter were selected, as suggested by Copeland[7], the ratio of patients with benign masses to patients with malignant masses would have fallen to 26·6 (Reference 7). Size alone was an imperfect criterion of malignancy but in this selected subgroup of patients with adrenal masses, larger masses were more likely to be malignant (*Table 1*). These data differ from those of Bertanga and Orth where in 58 patients with adrenocortical tumours, 31 had masses greater than 5 cm in diameter and seven were benign while 24 were malignant[23]. In the present study, however, the population included those cases sent for scintigraphy (NP-59 or mIBG) and patients with probable metastatic disease to the adrenals; an anticipated greater proportion of malignant adrenal masses due to the prediliction of the adrenal as a site(s) for metastatic involvement[24].

The adrenal masses were clinically 'silent' or 'incidental' in the majority (64 per cent) of patients – in nine of 11 patients with extra-adrenal malignancies (including two of three patients with lymphoma), five of ten patients with pain, and four of six patients with hypertension. Only six patients had clinical syndromes of adrenocortical dysfunction and five patients had pain which could reasonably be attributed to their tumours and one patient had a palpable abdominal (adrenal) mass.

In patients known to have primary, extra-adrenal malignancies, large adrenal masses do not necessarily represent metastases, especially if unilateral. Whereas the masses were metastatic in eight of the 11 patients with extra-adrenal malignancies, this was true in only two of the five patients with extra-adrenal malignancies and large, *unilateral* adrenal masses. Similarly, in our earlier survey of unilateral adrenal masses greater than 1 cm in diameter – all of which were 'incidental' – among 28 patients with known extra-adrenal primary malignancies, only one-third of the masses proved to be metastases[11]. The distinction is clinically important if an adrenal mass represents the only possible site of metastatic disease found during tumour staging, in which case the nature of the mass must be determined. Four of the eight patients in the present study with adrenal metastases (two unilateral, two bilateral) had large-cell, poorly differentiated bronchogenic carcinoma; neither patient with a unilateral adrenal metastases had any other evidence of extrathoracic metastases.

No combination of imaging modalities could be relied upon to 'prove' the nature of these large adrenal masses. In this series, the usual imaging criteria of malignancy were sensitive (86 per cent) but less specific (75 per cent) but these data include patients with bilateral metastases, a condition in which a normal adrenal is unavailable for scintigraphic comparison rendering scan interpretation more difficult. The bilateral absence of radiocholesterol uptake in a patient with bilateral masses would suggest bilateral metastatic involvement and perhaps adrenal hypofunction[11,22]. The only invariable sign of (metastatic) malignancy was bilateral disease (six of six cases) and these patients had clinical evidence of widespread disease. Among patients with primary adrenocortical tumours, radiological evidence of extracapsular and/or inferior vena cava invasion, and 'bilateral non-visualization' on radiocholesterol scintigraphy are likely to be specific for a hyperfunctioning, large, well-differentiated, adrenocortical carcioma, but only three of our seven patients with adrenal cortical carcinoma had one or more of these signs. Case 1 and the two patients with malignant, well differentiated aldosterone secreting tumours[19] had apparently encapsulated neoplasms on CT scans and sufficient NP-59 for visualization; the 'associated lymphadenopathy' in case 1 proved to be due to metastatic oesophageal carcinoma and the visualization of this mass may be due to its size. This contrasts with our previous experience with the entire spectrum of *non-hyperfunctioning*, but unilateral adrenal masses in which a concordant pattern of NP-59 uptake was invariably associated with benign pathology[11,12]. Although cases of *hyperfunctioning*, well differentiated malignant adrenocortical neoplasms, i.e. glucocorticoid and aldosterone-secreting, have imaged with iodocholesterol and the postoperative course of these patients was more akin to that expected of a patient with a benign neoplasm with subsequent biochemical normalization and cure[20,25]. The ability of a neoplasm to accumulate radiocholesterol appears to be to a large degree dependent upon its state of differentiation; well differentiated malignancies are more likely to accumulate sufficient NP-59 for visualization while less well differentiated lesions are not[21]. The clinical course of such patients can usually be predicted by the presence of NP-59 uptake as these lesions have a different, more benign course[24,25]. Rarely an adrenocortical carcinoma causing Cushing's syndrome may show good uptake of NP-59 and be associated with metastases and one cannot categorically imply a benign course based on a 'positive' scan[25]. Too few of the patients in this series underwent MRI to permit a detailed evaluation of this modality. Its ability to distinguish between benign and malignant adrenal masses has been disappointing in other studies[26,27,28].

None of the patients with adrenal cortical adenomas (four women, two men) had clinical or biochemical evidence of adrenal hyperfunction, although a 6 cm adrenal mass found incidentally in a 63-year-old man presenting with back pain and emphysema was later shown to exhibit autonomous glucocorticoid secretion. All four clinically hyperfunctioning tumours were malignant. The remaining three carcinomas were not clinically hyperfunctioning, although one showed slightly increased urinary 17-KS excretion; the other two patients were men with tumours measuring 10 cm and 19 cm in maximal diameter, neither of whom had clinical evidence of feminization although biochemical evidence of hyperestrogenism was not specifically sought. Thus five of seven 'non-hyperfunctioning', large, primary adrenal tumours were benign. Although large size is considered a reliable criterion of malignancy in functioning, primary adrenocortical tumours[5], it is by no means absolute. Androgen excess cannot be relied upon to make this distinction[5,29,30]. None of the patients with phaeochromocytomas had malignant neoplasms, despite their size, although given the predilection of these tumours to recur at times remote from their original diagnosis and the difficulty in distinguishing benign from malignant tumours on histological criteria alone demands careful long term follow-up and clinical vigilance[6,31,32].

None of the lymphomas in this series arose primarily in the adrenal. All three patients had diffuse histiocytic lymphoma and all had bilateral adrenal involvement. Macroscopic involvement of the adrenals evident on CT scans has been found in 1–4 per cent of patients with non-Hodgkin's lymphoma, with bilateral masses in about half the cases[33]. In case 7, bilateral adrenal uptake of ^{67}gallium citrate together with absent NP-59 uptake was, in the clinical setting, highly suggestive of bilateral adrenal lymphoma. Adrenal ^{67}gallium citrate uptake is not specific for lymphoma[34]. The presentation of case 8 with adrenal insufficiency was the first clue to recurrence of his lymphoma after a 2-year remission; lymphoma presenting with hypoadrenalism is unusual[35]. It is possible, although unproven, that adrenal insufficiency may have contributed to the terminal illness of case 7.

In conclusion, adrenal masses 5·0 cm or more in diameter are frequently but not invariably malignant. The larger the

mass, the more likely it is to be malignant, but no clinical, biochemical, radiologic or scintigraphic criteria are inveriably sensitive or specific to enable discrimination between benign and malignant large adrenal masses. In patients with primary extra-adrenal malignancies, bilateral large adrenal masses are highly likely to represent adrenal metastases[36] and other evidence of metastatic disease is usually apparent. In these cases it may be clinically more important to exclude adrenal insufficiency than to pursue the histological diagnosis of the masses[37]. Hyperfunctioning adrenal tumours require surgical treatment regardless of size. Large, non-hyperfunctioning, unilateral masses apparently confined to the adrenal were more likely to be benign (13 of 17 cases) than malignant: application of size recommendations to operate on such masses only if they exceeded 6 cm in diameter would have successfully identified all four malignancies in this series[7]. This study lends further support to such a relatively conservative approch, provided it is applied only in the last, highly selected, subgroup of patients. In the present series, although malignant adrenal masses were encountered more frequently, large benign adrenal masses were still two times more common.

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