Bilateral adrenal masses: a single-centre experience

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Abstract

Background: Bilateral adrenal masses may have aetiologies like hyperplasia and infiltrative lesions, besides tumours. Hyperplastic and infiltrative lesions may have coexisting hypocortisolism. Bilateral tumours are likely to have hereditary/syndromic associations. The data on clinical profile of bilateral adrenal masses are limited.

Aims: To analyse clinical, biochemical and radiological features, and management outcomes in patients with bilateral adrenal masses.

Methods: Retrospective analysis of 70 patients with bilateral adrenal masses presenting to a single tertiary care endocrine centre from western India (2002–2015).

Results: The most common aetiology was pheochromocytoma (40%), followed by tuberculosis (27.1%), primary adrenal lymphoma (PAL) (10%), metastases (5.7%), non-functioning adenomas (4.3%), primary bilateral macronodular adrenal hyperplasia (4.3%), and others (8.6%). Age at presentation was less in patients with pheochromocytoma (33 years) and tuberculosis (41 years) compared with PAL (48 years) and metastases (61 years) \((P < 0.001)\). The presenting symptoms for pheochromocytoma were hyperadrenergic spells (54%) and abdominal pain (29%), whereas tuberculosis presented with adrenal insufficiency (AI) (95%). The presenting symptoms for PAL were AI (57%) and abdominal pain (43%), whereas all cases of metastasis had abdominal pain. Mean size of adrenal masses was the largest in lymphoma (5.5 cm) followed by pheochromocytoma (4.8 cm), metastasis (4 cm) and tuberculosis (2.1 cm) \((P < 0.001)\). Biochemically, most patients with pheochromocytoma (92.8%) had catecholamine excess. Hypocortisolism was common in tuberculosis (100%) and PAL (71.4%) and absent with metastases \((P < 0.001)\).

Conclusion: In evaluation of bilateral adrenal masses, age at presentation, presenting symptoms, lesion size, and biochemical features are helpful in delineating varied underlying aetiologies.

Introduction

With increasing use of high-resolution imaging, incidentally found adrenal masses, mostly unilateral, are a common clinical problem. The vast majority of these unilateral masses are benign non-functioning adrenal adenomas \((1)\). Contrary to this, bilateral adrenal masses are uncommon, have varied clinical manifestations ranging from asymptomatic incidental findings to severe systemic clinical presentation and have varied aetiologies like bilateral adrenal hyperplasia, infiltration (infection, metastasis and lymphoma), and bilateral tumours like pheochromocytomas \((2, 3, 4)\).
Hypocortisolism is an exclusive feature to be considered in the evaluation of bilateral masses (3). Bilaterality of adrenal tumours points towards possibility of germline genetic defects (3). Hence, bilateral adrenal masses entail a somewhat different approach than that for unilateral masses. However, the literature on bilateral adrenal masses is scanty and limited to isolated case reports and a single case series of 18 patients (5).

We aimed to study the clinical, biochemical and radiological features, and management outcomes in our patients with bilateral adrenal masses. We propose a stepwise clinical approach for such patients.

Materials and methods

From 2002 to 2015, 560 patients with adrenal masses presented to a tertiary care endocrine centre in western India and 70 of them had bilateral masses (12.5%); these formed the current study cohort. After institutional ethics committee approval, medical records of 70 patients having bilateral adrenal masses were retrospectively analysed. The data retrieved from medical records (at baseline and on serial follow-up) included: clinical features, hormonal investigations, imaging details (anatomical and/or functional), management modalities and outcomes.

Basic biochemistry evaluation included 08:00h serum cortisol, plasma adrenocorticotropic hormone (ACTH), serum cortisol after overnight dexamethsone suppression test (ODST), plasma free metanephrines (PFMN) and normetanephrine (PFNMN) after 2008 and urinary vanillyl mandelic acid (VMA) before 2008. Hypocortisolism was defined as 08:00h serum cortisol < 137.5 nmol/L (5 μg/dL) and plasma ACTH levels more than two times of upper reference limit (46 pg/mL) (6). Dynamic stimulation testing could not be done due to non-availability of pharmacological preparations of short-acting ACTH in India. Hypercortisolism was defined as ODST serum cortisol ≥ 1.8 μg/dL. Plasma ACTH of < 10 pg/mL further classified these cases as ACTH-independent hypercortisolism. Screening test for pheochromocytoma was considered positive when urinary VMA > 10 mg/24h or PFMN > 90 pg/mL and/or PFNMN > 180 pg/mL. [123]I-metaiodobenzylguanidine (MIBG) scan (whenever feasible) was done to confirm the diagnosis of pheochromocytoma in suspected cases.

All patients underwent contrast-enhanced computerised tomography (CECT) of the abdomen. CECT was done as per predefined protocol which included basal, early venous (60s) and delayed (15 min) images for adrenal masses (whenever feasible). Radiological findings specific for certain masses such as adrenal cyst (0–20 Hounsfield units (HU) with no contrast enhancement) (7, 8), myelolipoma (heterogeneous masses with low-density –30 HU macroscopic fat) (9, 10), and adenoma (baseline HU ≤ 10, or benign washout patterns: absolute washout > 60% and relative washout > 40%) were considered diagnostic for the respective disorders. For non-secretory masses with equivocal imaging, additional clinical and radiological clues (extra-adrenal tuberculosis and evidence of primary malignancy) were looked for. Radiological evaluation for such cases included CECT (chest, abdomen and pelvis) and/or whole-body positron emission tomography with 2-deoxy-2-[18F]fluoro-o-glucose integrated with computed tomography (18F-FDG PET/CT). In absence any such clear association, adrenal biopsy was done for diagnosis. The biopsy sample was sent for routine microscopy, culture sensitivity (bacterial, tuberculosis and fungal culture) and histopathology.

Patients with pheochromocytomas or functional adenomas underwent laparoscopic adrenalectomy. Patients with non-functioning adenomas, cysts and myelolipoma underwent surgical resection, if lesion size exceeded 4 cm or else were observed with annual imaging. Patients with infections received appropriate antimicrobial therapy. Adrenal insufficiency (AI) was replaced adequately.

Assays

Before 2006, serum cortisol was assayed with a coated tube radioimmunoassay and plasma ACTH was assayed with an immunoluminescence assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). After 2006, serum cortisol was measured by a solid-phase competitive chemiluminescent enzyme immunoassay and plasma ACTH was assayed by a solid-phase, 2-site sequential chemiluminescent assay (Siemens Healthcare).

Metanephrines were determined using enzyme immunoassay (EIA) commercial kit manufactured by Labor Diagnostika (Nord GmbH, Nordhorn, Germany). The method used to detect urinary VMA was radioimmunoassay. Intraassay and interassay coefficients of variation were <8 and 10%, respectively, for all hormonal evaluation.

Statistical analysis

All continuous variables are presented as mean ± s.d. Categorical variables were expressed in actual number
and percentage. Age, sex and duration were compared between pheochromocytoma, tuberculosis, lymphoma and metastases by performing one-way analysis of variance (ANOVA) and t-test. All data analyses were performed using SPSS version 23.0 (SPSS).

Results

Medical records of 70 patients (42 males and 28 females) with bilateral adrenal masses were reviewed. Mean age at presentation was 39.7±16.1 years (range 11–72 years). Sixty-one patients (87.1%) had symptomatic presentation with average duration of symptoms being 15.0±19.1 months (range 0.25–92 months).

The underlying pathology in our cohort, in decreasing order of frequency, was pheochromocytoma (n = 28; 40%) followed by tuberculosis (n = 19; 27.1%), bilateral primary adrenal lymphoma (PAL) (n = 7; 10%), metastases (n = 4; 5.7%), non-functional adenomas (n = 3; 4.3%), PBMAH (n = 3; 4.3%) and other rare masses (n = 6; 8.6%). Other rare masses included two cases each with histoplasmosis and congenital adrenal hyperplasia (CAH) with myelolipoma, and one with cysts and one with leiomyoma.

Table 1 shows the baseline characteristics of this cohort.

Table 1 Characteristics of bilateral adrenal masses with various aetiologies.

<table>
<thead>
<tr>
<th></th>
<th>Pheochromocytoma</th>
<th>Tuberculosis</th>
<th>Lymphoma</th>
<th>Metastases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients: n (%)</td>
<td>28 (40%)</td>
<td>19 (27.1%)</td>
<td>7 (10%)</td>
<td>4 (5.7%)</td>
<td>–</td>
</tr>
<tr>
<td>Males: Females</td>
<td>13:15</td>
<td>15:4</td>
<td>6:1</td>
<td>3:1</td>
<td>0.023</td>
</tr>
<tr>
<td>Age (years) ± s.d.</td>
<td>33.2±16.5</td>
<td>41.5±12</td>
<td>48.8±12.5</td>
<td>61.5±8.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Range</td>
<td>(11–65)</td>
<td>(21–60)</td>
<td>(30–67)</td>
<td>(60–72)</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>19.1±18.7</td>
<td>18.6±25.1</td>
<td>3±2.3</td>
<td>5.2±2.2</td>
<td>0.16*</td>
</tr>
<tr>
<td>(months)± s.d. Range</td>
<td>(1–60)</td>
<td>(0.25–92)</td>
<td>(0.25–6)</td>
<td>(3–8)</td>
<td></td>
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<tr>
<td>Presenting symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Hyperadrenergic spell</td>
<td>15 (53.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. Hypocortisolism</td>
<td>0</td>
<td>18 (94.7%)</td>
<td>4 (57.1%)</td>
<td>0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>3. Abdominal pain</td>
<td>8 (28.5%)</td>
<td>1 (5.2%)</td>
<td>3 (42.8%)</td>
<td>4 (100%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>4. Asymptomatic</td>
<td>5 (17.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocortisolism</td>
<td>0</td>
<td>19 (100%)</td>
<td>5 (71.4%)</td>
<td>0</td>
<td>0.12*</td>
</tr>
<tr>
<td>CT features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean size (cm) ± s.d.</td>
<td>4.8±2.6</td>
<td>2.1±0.7</td>
<td>5.5±2.0</td>
<td>4±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>(1–15)</td>
<td>(1–4)</td>
<td>(2–8)</td>
<td>(3–5)</td>
<td></td>
</tr>
<tr>
<td>1. Right-sided lesions (cm) ± s.d.</td>
<td>4.7±2.4</td>
<td>2.2±0.6</td>
<td>4.8±2.1</td>
<td>3.9±0.8</td>
<td></td>
</tr>
<tr>
<td>2. Left-sided lesions (cm) ± s.d.</td>
<td>5±2.9</td>
<td>2.0±0.7</td>
<td>6.2±2.2</td>
<td>4.2±0.5</td>
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</table>

s.d., Standard deviation.

*The difference in the age at presentation and duration of symptoms for pheochromocytoma and tuberculosis, in comparison with that of lymphoma and metastases were statistically significant by student t-test; 5Significant between tuberculosis and lymphoma; 6Significant between pheochromocytoma and tuberculosis, tuberculosis and lymphoma, metastasis and all other groups together; 7Not significant in between any pair of pathologies.

Bilateral pheochromocytoma (n =28; 13 males, 15 females)

Patients with pheochromocytoma presented at mean age of 33.2±16.5 years (range 11–65 years). Symptomatic presentation with hyperadrenergic spells (n=15) and abdominal pain (n=8) was more common than asymptomatic detection (n=5). Mean duration of symptoms was 19.1±18.7 months (1–60 months). Among asymptomatic patients, 3 cases (von Hippel–Lindau syndrome (VHL): 2 and multiple endocrine neoplasia 2A (MEN2A): 1) were detected on familial screening, and 2 cases were incidentally found. Most patients (n=21, 75%) had syndromic/familial associations while 7 were apparently sporadic. In the former group, 17 patients from 10 families had syndromic associations (VHL: 11 in 5 families, MEN2A: 4 in 3 families and MEN 2B: 2 in 2 families) and 4 patients had family history of pheochromocytoma without syndromic characteristics. Limiting analysis to index cases, 14/21 (66.6%) patients with bilateral pheochromocytomas had syndromic/familial association. In 19 patients, where plasma metanephrines were available, 13 had isolated elevation of PFNMN and 6 had elevation of both PFMN and PFNMN. Urinary VMA was available in remaining 9 patients and was elevated in 7 of them. In 2 patients with negative urinary VMA, MIBG scan was positive and histopathology confirmed
diagnosis of pheochromocytoma. On CT imaging, mean lesion size was $4.8 \pm 2.6$ cm (range 1–15 cm) with baseline HU $>10$ (Fig. 1A). In 16 masses, where all phases of CT as per adrenal protocol were available, mean baseline HU was 39 (range 13–61) and 70% had poor washout. MIBG was available in 22 patients and all of them showed MIBG avid lesions in bilateral adrenals. Twenty-two patients underwent bilateral adrenalectomy (cortical sparing: 4 cases) and received adequate glucocorticoid and mineralcorticoid replacements. Operated cases were asymptomatic at mean follow-up of $22.2 \pm 20.6$ months after surgery. In remaining 6 patients, 2 are awaiting surgery, 2 refused surgery and 2 are lost to follow-up. In these 6 patients, metanephrines/urinary VMA were raised and MIBG was positive.

**Bilateral adrenal tuberculosis ($n=19$; 15 males, 4 females)**

Patients with bilateral adrenal tuberculosis presented at mean age of $41.5 \pm 12$ years (range 21–60 years). All patients had symptomatic presentation with a mean duration of $18.6 \pm 25.1$ months (range 0.25–92 months). Clinical presentation was due to symptoms of AI in all except one who presented with abdominal pain. Biochemically all had AI. On CT, mean lesion size was $2.1 \pm 0.7$ cm (range 1–4 cm) (Fig. 1B). Ten patients (52.6%) had evidence of adrenal calcification (unilateral and/or bilateral). Twelve (63.1%) patients had evidence of extra-adrenal tuberculosis (pulmonary, 8; abdominal lymphadenopathy, 2; cervical lymphadenitis, 1; and epididymo-orchitis, 1). Cases without evidence of extra-adrenal tuberculosis ($n=7$) were subjected to CT-guided biopsy of adrenals and had epitheloid granulomas and positive culture for mycobacterium tuberculosis. All patients received anti-tuberculosis treatment, which was adequately replaced with glucocorticoid and mineralocorticoids. All patients were asymptomatic at $39.1 \pm 35$ months of clinical follow-up. AI was permanent in all patients.

**Bilateral PAL ($n=7$; 6 males, 1 female)**

Patients with PAL presented with mean age of $48.85 \pm 12.5$ years (range 30–67 years). All were symptomatic with a mean duration of $3 \pm 2.3$ months (range 0.25–6 months). Four patients presented with symptoms of...
AI and other three had abdominal pain. Hypocortisolism was seen in 5/7 cases, while mineralocorticoid axis involvement (manifested as hyponatraemia and hyperkalaemia) was seen in 4 of them. On CT imaging mean lesion size was 5.5 ± 2.0 cm (range 2–8 cm). In 6 masses where all phases of CT as per adrenal protocol were available, mean baseline HU was 32 (range 28–35) and poor washout pattern was observed in all (Fig. 1C). FDG PET CT was available for 5 patients, which showed isolated bilateral adrenal uptake. On imaging-guided biopsy, all patients had non-Hodgkin’s lymphoma (B cell type in 5 and T cell type in 2) and were managed with SMILE chemotherapy (steroid: dexamethasone, methotrexate, ifosfamide, l-asparaginase and etoposide) regimen. Four patients had remission at median follow-up of 4 months (range 0–4 months), two patients succumbed to the disease and one was lost to follow-up.

**Bilateral adrenal metastases (n = 4; 3 males, 1 female)**

Patients with bilateral adrenal metastases presented with mean age of 61.5 ± 8.3 years (range 60–72 years). None of the patients were previously known to harbour malignancy. All patients were symptomatic with abdominal pain with mean duration of 5.2 ± 2.2 months (range 3–8 months) and were normocortisolaemic. On CT imaging, mean lesion size was 4.0 ± 0.6 (range 3–5 cm). In 4 masses, where all phases of CT as per adrenal protocol were available, mean baseline HU was 38 (range 20–46) and all had poor washout pattern (Fig. 1D). On evaluation, 3 patients had evidence of primary malignancy (lung carcinoma on CT: 2 and biopsy-proven gastric adenocarcinoma: 1) while in one patient, adrenal biopsy was suggestive of melanoma but primary remained occult despite evaluation. These patients were referred to oncology centre for pathology-specific management.

**Bilateral adrenal adenomas (n = 3; 1 male, 2 females)**

Patients with bilateral adrenal adenomas presented with mean age of 37.3 ± 9.6 years (range 27–46 years). Two patients were known cases of multiple endocrine neoplasia type 1 (MEN 1) syndrome and adrenal adenomas were detected during imaging for screening of MEN 1-related syndromic components. The third patient was incidentally detected. Normocortisolism was documented in all cases, and masses were non-secretory. On CT, mean lesion size was 2.3 ± 0.6 cm (range 1.5–3.3 cm). The masses remain non-secretory and static on serial imaging at mean follow-up of 43 months (Fig. 1E).

**PBMAH (n = 3; 1 male, 2 females)**

Patients with PBMAH presented with mean age of 51.0 ± 13.7 years (range 36–60 years). All three patients were asymptomatic with lesions diagnosed incidentally on imaging. On CT, mean lesion size was 3.0 ± 0.87 cm (range 1.5–4 cm) and masses were irregular (Fig. 1F). Biochemically, all had subclinical adrenal Cushing’s syndrome. The patients remained asymptomatic, and biochemistry and mass size remained static at mean a follow-up of 32 months.

**Other masses**

**Histoplasmosis (n = 2; 1 male, 1 female)** One of the patients, a 47-year-old man was diagnosed to have bilateral adrenal masses (right 5 cm, left 6.2 cm) on evaluation for symptoms of AI. Biopsy was suggestive of histoplasmosis on histopathological and microbiological examination. He had a history (18 months) of untreated laryngeal histoplasmosis. He was noncompliant to medical treatment and succumbed to adrenal crisis. Other patient, a 60-year-old woman presented with symptoms of AI and bilateral adrenal masses (right 5.8 cm, left 6.5 cm). As patient had a history of pulmonary tuberculosis, she underwent antituberculosis treatment. However, due to persistent symptoms, she was subjected to adrenal biopsy and diagnosed to have histoplasmosis. With antifungal medications (IV amphotericin B followed by oral itraconazole), there was regression of adrenal masses (right 4.4 cm, left 3.8 cm) at 19-month follow-up (11).

**Myelolipoma (n = 2; both males)** Both the patients had CAH (11β-hydroxylase deficiency) and masses were detected during hypertension workup. CT features were diagnostic of myelolipoma. Both were managed medically.

**Cysts (n = 1)** This patient had incidental detection of bilateral adrenal cysts (right 5 cm, left 3 cm with wall calcification). She was asymptomatic and had normal biochemistry. She underwent unilateral cyst excision (due to larger cyst size on right side) for histopathological diagnosis. Histopathology revealed lymphoendothelial cyst. The contralateral cyst remained static on serial imaging at 1 year.

**Leiomyoma (n = 1)** One patient (11 years, female) presented with abdominal pain and had bilateral
adrenal masses (right 8 cm, left 3 cm). These were bilateral leiomyomas on histopathology. The patient remained asymptomatic at 3-year follow-up.

**Histopathological diagnosis (n=40)**

As per our methodology, diagnosis of patients with secretory masses could be made on the basis of secretory profile (e.g. pheochromocytoma and PBMAH) and were not subjected to biopsy. However, most patients with pheochromocytoma (22/28) were operated and histopathological diagnosis was available. For non-secretory masses, histopathological confirmation of diagnosis was sought only in patients with equivocal radiological findings and no additional clinical and radiological clues (extra-adrenal tuberculosis and evidence of primary malignancy). On following this protocol, biopsy was required for 18 patients (7 patients with lymphoma, 7 with tuberculosis, 2 with histoplasmosis, and one each with metastasis and cytis). In one patient with leiomyoma, diagnosis was established on post-operative histopathology. To summarise, histopathological diagnosis was established in 41 patients.

**Discussion**

In our cohort of 70 patients with bilateral adrenal masses, the underlying pathology was pheochromocytoma (40%) followed by tuberculosis (27.1%), lymphoma (10%), metastases (5.7%), adenomas (4.3%) and other rare masses (histoplasmosis, myelolipoma, cysts and leiomyoma).

The approach to bilateral adrenal masses differs from that of unilateral masses due to some differences in underlying aetiologies, greater role of genetics in bilateral tumours and consideration of AI in management of these patients (3). However, literature on bilateral adrenal masses is limited to case reports and a single series of 18 patients (5). Hence, the systematic approach to patients with bilateral adrenal masses remains to be defined. Our series is the largest reported series of bilateral adrenal masses to the best of our knowledge and provides an overview of clinical presentation, evaluation and management of this uncommon disorder.

We compared our results with that described by Zhou and coworkers (5) (the only histopathologically confirmed other series reported) (Table 2). Despite difference in sample size, the two cohorts were comparable in baseline characteristics. Similar to our findings, pheochromocytoma was the leading diagnosis and lymphomas presented with the largest tumour size in their cohort as well. However, a striking difference is the lower incidence of bilaterality in the overall subset of patients with adrenal masses in their cohort (18/565, 3.2%) compared with our cohort (70/560, 12.5%). The reason for this disparity remains unknown. Another difference is the absence of non-neoplastic aetiologies like cysts and infections in their cohort which might be attributable to small sample size. Authors have attributed absence of adrenal tuberculosis to its declining incidence (5). We have also noticed the declining incidence of adrenal tuberculosis, as majority (15/19) of the adrenal tuberculosis cases presented before year 2007. Nevertheless bilateral adrenal tuberculosis continues to be a common cause of AI in developing world (12).

Bilateral pheochromocytomas, the leading diagnosis in our cohort, are known to have familial and/or syndromic association. In a study of 314 patients, Amar and coworkers reported significantly greater familial and/or syndromic association (31/41, 75.6%) in patients with bilateral pheochromocytomas, compared with those with unilateral pheochromocytomas (49/223, 21.9%) (13). Similarly, two-thirds (14/21) of our index patients with bilateral pheochromocytomas had familial/syndromic association. Diagnosis of pheochromocytoma could be made biochemically as all, except two, had evidence of catecholamine excess. These two patients with histopathologically proven diagnosis had normal urinary VMA. This exemplifies the well-described lower sensitivity of urinary VMA compared with that of PFMN and PFNMN (64% vs 100%) (14).

Adrenal tuberculosis was the second leading diagnosis in our cohort. The mean adrenal size in our cohort was 2.1 ± 0.7 cm (range 1.0–4.0 cm) and 10 patients (52.6%) had a common cause of AI in developing world (12).

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**Table 2** Comparison of our study with that of Zhou and coworkers (5).

<table>
<thead>
<tr>
<th>Study</th>
<th>Jiaqiang Zhou and coworkers (5)</th>
<th>Our series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>Proportion of bilateral masses among all adrenal tumours</td>
<td>3.2%</td>
<td>15%</td>
</tr>
<tr>
<td>Age (years) ± s.d.</td>
<td>43.0 ± 17.1</td>
<td>39.7 ± 16.1</td>
</tr>
<tr>
<td>Sex</td>
<td>11 males, 7 females</td>
<td>42 males, 28 females</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>6 (33.3%)</td>
<td>28 (40%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Not seen</td>
<td>19 (27.1%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4 (22.2%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Metastases</td>
<td>2 (11.1%)</td>
<td>4 (5.7%)</td>
</tr>
<tr>
<td>Adenoma</td>
<td>4 (22.2%)</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (11.1%)</td>
<td>9 (12.8%)</td>
</tr>
</tbody>
</table>
had evidence of adrenal mass calcification (unilateral and/or bilateral). Our findings are similar to that of Guo and coworkers who reported 90% of their cohort of 42 patients with adrenal tuberculosis to have bilaterally enlarged adrenals with mean size of 2.0 ±1.0 cm (range 0.9–4.5 cm) in right, 2.1±1.2 cm (range 1.0–6.2 cm) in the left and evidence of calcification in 50% patients (12). All our patients had evidence of AI. In patients with bilateral adrenal masses having AI, it has been suggested that evidence of extra-adrenal tuberculosis obviates the need of adrenal biopsy (15). Following a similar conservative approach, we needed biopsy in only one-third of our patients. However, one patient with adrenal histoplasmosis was initially mistreated with anti-tuberculosis drugs before the true diagnosis was revealed and then adrenal biopsy done for non-response to anti-tuberculosis treatment. The conservative approach causing delay in diagnosis and potential mistreatment has also been described previously (5). This case emphasises caution for this approach. Another concern that makes biopsy important is the fact that 12% of patients may not have evidence of extra-adrenal tuberculosis (16).

Bilateral PAL constituted the third common diagnosis in our cohort, and four patients have been a part of the previously published cohort from our centre (17). The characteristics of our patients with PAL were similar to those described by Rashidi and coworkers in their systematic review of 187 PAL patients (18). Similar to their description, we found that our PAL cohort was older with male predominance (Male: Female 3.0 in our series vs 1.8 in their review), symptomatic presentation (severe pain and AI), large masses (mean size 5.5 cm in our series vs 8 cm in their review), mild to moderate contrast enhancement on CT, and presence of AI (71% in our series vs 61% in their review).

Adrenal metastases were uncommon in our series (5%). The incidence of adrenal metastasis is understandably higher (30–70%) in oncology series than in non-oncology series (0–20%) (19). None of the patients in our cohort had a history of malignancy. This might explain the lower incidence in our series as those patients with adrenal masses and a known primary tumour may not have been referred to us, especially in absence of AI. In our series, the primary tumour remained occult after evaluation in one patient. All four patients with adrenal metastases (mean size 4 cm) were incidentally detected, when imaged for abdominal pain and none had AI at presentation. The rarity of AI in patients with bilateral adrenal metastasis is also reported by Lam and coworkers in their large cohort of 464 patients with adrenal metastasis (50% bilateral), wherein they found incidence of AI to be <2%. However, the mean size of lesions in their cohort was 2 cm (19). Radiological differentiation from adenomas was possible in these patients as they had poor contrast washout at delayed imaging. Less prevalence of adenomas in our cohort can be explained by the referral bias.

Ours being a tertiary care endocrine centre, patients with large symptomatic adrenal masses could have been referred preferentially. On sub-analysis, we found certain characteristics, namely age, symptomatic presentation, duration of symptoms, nature of symptoms, biochemical cortisol status and lesion size tend to segregate and suggest specific diagnosis. Patients with pheochromocytoma/tuberculosis were significantly younger than those with lymphoma/metastases (Fig. 2A). Overall symptomatic presentation was more common with incidental asymptomatic presentation seen only in patients with PBMAH, cysts and familial patients with pheochromocytoma who were detected during
screening. Patients with pheochromocytoma/tuberculosis had longer duration of symptoms (weeks to months) compared with those with lymphoma/metastases (months to years) (Fig. 2B). Nature of symptoms was variable with most patients with pheochromocytoma (except those diagnosed through family screening) having hyperadrenergic spells and/or abdominal pain. Symptoms of AI were seen in almost all patients with infective masses (tuberculosis and histoplasmosis) and half of patients with lymphomas. Abdominal pain was the presenting symptom in patients with metastasis, lymphomas and few patients with pheochromocytoma. Biochemically hypercortisolism was seen only in patients with PBMAH, while hypocortisolism was documented in all patients with infective masses and some patients with lymphoma. Notably, none of the patients with metastasis had AI. Smaller size of mass was seen in tuberculosis (2.1 cm) compared with that seen in lymphoma (5.5 cm), pheochromocytoma (4.8 cm) and metastasis (4 cm) (Fig. 2). Bilateral adenomas were incidentally detected and were non-secretory. Despite these suggestive features, no single or combination of clinical parameters could meet the statistical requirement to derive a clinical score to suggest a non-invasive pre-operative diagnosis. Hence our attempt to suggest a clinical algorithm for approach to bilateral masses is influenced by that for unilateral adrenal incidentaloma. Since the secretory nature and malignancy are the two features which call for surgical intervention, the first step in evaluation should be a detailed history, relevant family history (for genetic syndromes associated with pheochromocytomas) and physical examination to look for the evidence of hormonal oversecretion, infection or malignancy. Hypersecretory masses should be managed according to respective diagnosis. In hypoor normocortisolaemic patients, CT characteristics suggestive of specific diagnosis should guide treatment. In absence of these, other systemic evidence for extra-adrenal tuberculosis or primary malignancy should be looked for. Adrenal biopsy should provide the diagnosis in remaining cases. Figure 3 depicts the suggested algorithm to approach bilateral adrenal masses.

Our study has certain limitations. The retrospective nature of the study and the fact that the patients included were seen over a long period of time have led to heterogeneity in certain biochemical (catecholamines) and radiological parameters (absence of adrenal protocol CECT in many patients). Another limitation was absence of follow-up CT studies to demonstrate resolution in adrenal tuberculosis. Absence of aldosterone axis evaluation (not done in in-house laboratory) is another limitation. However, all the hypertensive patients in our cohort had pheochromocytoma and in remaining patients, specific diagnosis was reached in all except three patients with adenomas (normotensive) where aldosterone axis evaluation should have not been done. Primary aldosteronism is a cause of adrenal incidentaloma in less than 1% of patients, and the incidence is expected to be further lower in bilateral masses cohort. Nevertheless, aldosterone axis evaluation should be a part of workup of hypertensive patients with adrenal masses (20).

Figure 3
Approach to bilateral adrenal masses. ACTH: adrenocorticotropic hormone, CT: computerized tomography, ODST: oral dexamethasone suppression test, PBMAH: primary bilateral macronodular adrenocorticotrophic hyperplasia.
In conclusion, aetiology of bilateral adrenal masses in non-oncology endocrine centre is commonly pheochromocytomas followed by tuberculosis, lymphomas, metastases and adenomas. Pheochromocytomas present at younger age with hyperadrenergic spells. Bilateral pheochromocytomas strongly point towards familial/syndromic association. Adrenal tuberculosis has prolonged symptomatic presentation with prominent features of AI and has smaller masses which may be calcified. Lymphoma presents in older males with short duration of abdominal pain with/without AI and larger size on imaging. Symptomatic presentation of short duration and absence of AI point towards metastases. Incidental detection, non-secretory nature and static small dimensions are a feature of adenomas. In evaluation of bilateral adrenal mass, age at presentation, presenting symptoms, lesion size and biochemical features are helpful in delineating varied underlying aetiologies.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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