Differences Between Bilateral Adrenal Incidentalomas and Unilateral Lesions

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**IMPORTANCE** Adrenal incidentalomas are found in 1% to 5% of abdominal cross-sectional imaging studies. Although the workup and management of unilateral lesions are well established, limited information exists for bilateral incidentalomas.

**OBJECTIVE** To compare the natural history of patients having bilateral incidentalomas with those having unilateral incidentalomas.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective analysis of a prospective database of consecutive patients referred to an academic multidisciplinary adrenal conference. The setting was a tertiary care university hospital among a cohort of 500 patients with adrenal lesions between July 1, 2009, and July 1, 2014.

**MAIN OUTCOMES AND MEASURES** Prevalence, age, imaging characteristics, biochemical workup, any intervention, and final diagnosis.

**RESULTS** Twenty-three patients with bilateral incidentalomas and 112 patients with unilateral incidentalomas were identified. The mean age at diagnosis of bilateral lesions was 58.7 years. The mean lesion size was 2.4 cm on the right side and 2.8 cm on the left side. Bilateral incidentalomas were associated with a significantly higher prevalence of subclinical Cushing syndrome (21.7% [5 of 23] vs 6.2% [7 of 112]; \( P = .009 \)) and a significantly lower prevalence of pheochromocytoma (4.3% [1 of 23] vs 19.6% [22 of 112]; \( P = .003 \)) compared with unilateral lesions, while rates of hyperaldosteronism were similar in both groups (4.3% [1 of 23] vs 5.4% [6 of 112]; \( P > .99 \)). Only one patient with bilateral incidentalomas underwent unilateral resection. The mean follow-up was 4 years (range, 1.2-13.0 years). There were no occult adrenocortical carcinomas.

**CONCLUSIONS AND RELEVANCE** Bilateral incidentalomas are more likely to be associated with subclinical Cushing syndrome and less likely to be pheochromocytomas. Although patients with bilateral incidentalomas undergo a workup similar to that in patients with unilateral lesions, differences in their natural history warrant a greater index of suspicion for subclinical Cushing syndrome.
ncidentally discovered adrenal lesions, or incidentalomas, continue to be a clinical conundrum. The prevalence of these lesions has been reported to be as high as 1% to 5% of abdominal cross-sectional imaging studies performed for reasons unrelated to the adrenal gland.\textsuperscript{1-4} Once an incidentaloma is discovered, its functional status and malignant potential should be evaluated. Multiple organizations have published guidelines outlining the evaluation of adrenal incidentalomas.\textsuperscript{4,5} Surgery is generally recommended for larger or growing lesions, as well as those with hormonal hypersecretion. Although the workup of bilateral and unilateral incidentalomas is similar, the results of small studies\textsuperscript{5,6} suggested differences in the two groups. We sought to determine the characteristics and natural history of patients having bilateral adrenal incidentalomas to provide greater insight into their workup and management.

Methods

Patient Selection
We conducted a retrospective analysis of a prospectively collected database of consecutive patients referred to a tertiary care multidisciplinary adrenal conference at the University of California, San Francisco (UCSF) Medical Center. Patients evaluated within a 5-year period between July 1, 2009, and July 1, 2014, were reviewed. All patients with a referral to clinical endocrinology or endocrine surgery were automatically reviewed by a multidisciplinary adrenal conference consisting of endocrine surgeons, endocrinologists, and radiologists. Patient medical records were evaluated for demographics, adrenal lesion characteristics, functionality, intervention (if any), and outcome. Patients with adrenal incidentalomas were those who underwent imaging unrelated to adrenal disease or active surveillance for cancer. Those patients being screened for adrenal manifestations of genetic syndromes were not included in the analysis. The UCSF Committee on Human Research, the university’s institutional review board, approved the study protocol. The protocol was for medical record review and required no additional written or verbal consent beyond the general consent already signed by all patients treated at the UCSF Medical Center.

Determination of Adrenal Incidentaloma Functional Status
All patients underwent screening for pheochromocytoma and primary aldosteronism according to published guidelines.\textsuperscript{4,5} To screen for pheochromocytoma, all patients had plasma free metanephrines measured. Collection of 24-hour urinary fractionated metanephrines was used as an adjunct for patients with diagnostic uncertainty. Screening for hypersecretion of aldosterone included the ratio of plasma aldosterone to plasma renin and (in some patients) 24-hour urinary aldosterone measurement. These patients underwent further biochemical workup, including plasma potassium and renal function testing. Because these patients had bilateral lesions, positive testing for primary aldosteronism necessitated adrenal venous sampling.

To screen for hypercortisolism, patients underwent an overnight 1-mg dexamethasone suppression test, 24-hour urinary free cortisol test, or morning cortisol and corticotropin testing depending on the preferred modality of the referring endocrinologist. A diagnosis of asymptomatic hypercortisolism or subclinical Cushing syndrome (SCS) was made if at least 1 of the following 3 criteria were met: (1) cortisol level after dexamethasone suppression test exceeding 1.8 μg/dL (to convert cortisol level to nanomoles per liter, multiply by 27.588), (2) 24-hour urinary free cortisol exceeding 50 μg, or (3) multiple low corticotropin levels, suggesting pituitary suppression. In addition, one patient had a midnight salivary cortisol measurement (upper limit of normal, 0.09 μg/dL). The differential diagnosis for patients with bilateral nonsecreting lesions includes benign adenomas or adrenocortical carcinomas (more likely unilateral),\textsuperscript{9,10} and those found to have hypersecretion underwent further localization using a combination of imaging and adrenal venous sampling if surgery was planned. If there was any concern about the accuracy of diagnosis or regarding malignancy, the patient had repeat imaging and biochemical testing at 3-month to 12-month follow-up.

Statistical Analysis
Statistical analysis was performed using statistical software (STATA, version 9; StataCorp LP). Comparisons of proportions were conducted using Fisher exact test.

Results
Five hundred new patient referrals were presented at the multidisciplinary adrenal conference during the study period. Of this total, 135 patients had adrenal incidentalomas, 23 of whom had bilateral lesions. In this bilateral cohort, the mean age at diagnosis was 58.7 years, and 56.5% (13 of 23) of patients were women. The mean follow-up was 4 years (range, 1.2-13.0 years).

Table 1 summarizes the characteristics of the patient cohort.
None of the patients with SCS underwent adrenalectomy, in other words, differences in HU densities (Figure). The patient underwent initial imaging after being seen with unrelated hematopoietic disease. Biochemical workup of this patient showed elevated plasma free metanephrines and 24-hour urinary fractionated metanephrines, with normal 24-hour urinary free cortisol and a normal ratio of plasma aldosterone to plasma renin. The patient with primary aldosteronism had data from adrenal venous testing that suggested bilateral disease, so adrenalectomy was not performed. Those with SCS were serially followed up for any symptoms or worsening biochemical findings. For various reasons, none of the patients with SCS underwent adrenalectomy, including patient preference, minimal or absent symptoms or sequelae of overt Cushing syndrome, or loss to follow-up.

**Discussion**

We report the results of a retrospective review of 135 patients with incidentalomas among 500 patients with adrenal disease evaluated at a tertiary care multidisciplinary adrenal conference. Of 135 patients with adrenal incidentalomas, 17.0% (23 patients) had bilateral lesions. This finding is in agreement with other large population series, which found up to 23% bilateral prevalence. While there are many studies and guidelines for the evaluation of patients with adrenal incidentalomas, we focused specifically on those with unilateral lesions.

In our series, we demonstrated a higher prevalence of SCS among patients with bilateral incidentalomas. Other small series found similar results. To determine whether one side may be dominant in cortisol secretion, Young et al used adren venous testing, with resultant surgical intervention that led to some biochemical or clinical improvement. Iodomethyl-19-norcholesterol scintigraphy is not available for use in the United States. In this series, only one patient with a pheochromocytoma underwent unilateral resection. The side of resection was determined based on computed tomography criteria (Figure).

None of 5 patients with SCS underwent adrenalectomy. For those patients who met size criteria for resection (>3 to 5 cm, de-

**Table 2. Imaging Characteristics of 23 Patients With Bilateral Incidentalomas**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidentaloma</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion size, mean (SD), cm</td>
<td></td>
<td>2.4 (1.2)</td>
<td>2.8 (1.6)</td>
</tr>
<tr>
<td>Density, median (range), Hounsfield units</td>
<td>14.8 (1-23)</td>
<td>12.1 (0-36)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis based on imaging, No. (%)</td>
<td>Adenoma</td>
<td>17 (73.9)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td></td>
<td>Myelolipoma</td>
<td>0</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td>0</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td></td>
<td>Adrenocortical carcinoma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>6 (26.1)</td>
<td>3 (13.0)</td>
</tr>
</tbody>
</table>

The scale shows density in Hounsfield units. R indicates right.
pending on patient age and comorbidities and tumor characteristics on imaging studies), patient preference for observation was taken into consideration. In the patients with SCS and hypertension or obesity, the degree of hypercortisolism was determined to be mild and unlikely to be responsible for these manifestations. The morbidity of bilateral adrenalectomy is as high as 18%,14,15 There is evidence to suggest that SCS may be undertreated.19 However, studies have largely been retrospective and heterogeneous in the definition of SCS and with regard to desired clinical outcome goals.20 One prospective randomized study21 showed improved outcome in patients with SCS who underwent laparoscopic resection of unilateral adrenal incidentalomas compared with those who had nonsurgical follow-up. However, patients with bilateral lesions are more complex because the laterality of cortisol hypersecretion must be determined before surgical intervention. The physician must weigh the risks of adrenalectomy by considering inadequate long-term randomized data showing improved outcome after surgery in this group of patients.19,22

There are several limitations to this study. First, it was dependent on a retrospective analysis, with its well-known drawbacks. Second, patients included in this study were referred to a tertiary care university medical center, which may be associated with a selection bias in that this cohort does not represent the overall population of patients with bilateral incidentalomas. However, this bias is somewhat mitigated because both medical and surgical endocrinologists were the sources of referral. In other words, the adrenal conference was not limited to just those referred for surgery. Third, patients in this series had a short follow-up, with a mean of 4 years. Longer follow-up may demonstrate that some patients with SCS will indeed require adrenalectomy because of worsening hypercortisolism or tumor growth. Larger series and longer follow-up will be needed to evaluate the long-term natural history of this population. Fourth, not all of our patients underwent the same testing for hypercortisolism, which led to variability in the diagnostic criteria for SCS. Other groups may have different criteria. Nevertheless, the overall result is consistent with other studies that suggest a higher prevalence of SCS among patients with bilateral incidentalomas. We recommend a standardized workup protocol for SCS in patients with incidentalomas (whether unilateral or bilateral) so as to have more uniform biochemical definition of SCS. This evaluation should include 24-hour urinary free cortisol, an overnight 1-mg dexamethasone suppression test, and morning cortisol and corticotropin testing. Some patients with bilateral incidentalomas and SCS may be candidates for surgery because of size and imaging characteristics of the tumors or the results of adren venous testing.

Conclusions

Bilateral adrenal incidentalomas are common, occurring in 23 of 135 patients (17.0%) with adrenal incidentalomas in this series. Recommended workup and surgical indications for patients with bilateral incidentalomas are similar to those for patients with unilateral lesions. In this series, 5 of 23 patients (21.7%) with bilateral incidentalomas had SCS.
Bilateral Adrenal Incidentalomas vs Unilateral Lesions

Nonoperative Management of Bilateral Adrenal Incidentalomas
The Value of Restraint

Linwah Yip, MD; Sally E. Carty, MD

Incidentally identified adrenal nodules are seen bilaterally in as many as 17% of patients as reported in Pasternak et al. The management of patients with bilateral incidentalomas presents a clinical challenge and is optimized with a multidisciplinary and experienced approach that is highlighted beautifully in this high-volume tertiary-center study.

All study patients were evaluated in a multidisciplinary forum inclusive of endocrinologists, endocrine surgeons, and radiologists. Using an objective algorithmic approach, Pasternak et al found that 30% of patients with bilateral incidentalomas had hormonal hypersecretion. Compared with unilateral incidentalomas, bilateral incidentalomas were particularly associated with a significantly higher prevalence of subclinical Cushing syndrome (21.7% vs 6.2%). Because of the presence of bilateral adrenal lesions, none of the patients have yet had surgical treatment and follow-up is ongoing, but the results suggest that, with a mean follow-up of 4.6 years, a benign course is the rule and that mild hypercortisolism does not progress discernably. The natural history of patients with asymptomatic hypercortisolism is poorly understood as a result of the imprecise thresholds used to define autonomous hypercortisol production and owing to ill-defined outcome measures. The study results thus also emphasize that better quality data for patients with subclinical Cushing syndrome will be essential to guide future management algorithms, including indications for surgery when both adrenals are incidentally abnormal on imaging.

Also very laudable in this report is the use of adrenal imaging enhancement characteristics to guide appropriate surgical management of patients with pheochromocytoma and bilateral adrenal lesions. Adrenal imaging characteristics (including low-density on unenhanced computed tomography, the rapid washout of contrast on computed tomography with delayed imaging) have been shown to be highly associated with benign, lipid-rich adenomas. The interpretation of these imaging features should be a routine component of the evaluation of adrenal lesions and, in Pasternak et al, allowed for the lateralization of a pheochromocytoma to the left side while avoiding the use of costly and often unnecessary additional imaging, such as metaiodobenzylguanidine scintigraphy.

The evaluation of patients with bilateral adrenal incidentalomas is considerably more nuanced than the evaluation of patients with an isolated unilateral incidentaloma. Surgery is not always indicated even with biochemical documentation of hormonal hypersecretion. A multidisciplinary approach can help us appropriately identify those patients who do require an adrenalectomy, and the findings of this report exemplify objectively that restraint can often be the better part of valor.

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Invited Commentary

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Conflict of Interest Disclosures: None reported.

REFERENCES