Adrenal ganglioneuromas: Incidentalomas with misleading clinical and imaging features

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Background. Ganglioneuromas are benign neoplasms of the neural crest, occurring rarely in the adrenal glands. This study presents our experience regarding diagnostic and therapeutic management of these neoplasms and a review of the relevant literature.

Methods. Among 150 patients with incidentalomas, we had 7 primary ganglioneuromas. Their clinical, imaging, and operative data were collected retrospectively, and the literature was reviewed using MEDLINE. There were 4 females and 3 males, with mean age of 50 years (range, 39–64). All neoplasms were discovered incidentally with ultrasonography and were evaluated subsequently with computed tomography (CT). One patient was studied further with 131I-MIBG due to asymptomatic increased in urine vanillylmandelic acid, and 1 patient with history of breast cancer underwent additional FDG-PET/CT.

Results. All but 2 patients were asymptomatic. Two patients complained of epigastric pain and hypertension, respectively. The preoperative mean size on CT was 6.8 cm, whereas the postoperative true mean histologic size was 7.7 cm. Both patients who were evaluated with radionuclide studies had false positive results, suggestive of pheochromocytoma and adrenal metastasis, respectively. Three patients underwent open adrenalectomy due to preoperative suspicion of carcinoma, and the remaining 4 underwent laparoscopic anterior adrenalectomy. Histologically, all 7 neoplasms were completely differentiated, mature ganglioneuromas. We had no mortality or significant morbidity. No recurrence occurred during a mean follow-up of 6 years (range, 1–18).

Conclusion. Adrenal ganglioneuromas are rare incidentalomas that can mimic primary or secondary adrenal malignancies as well as pheochromocytomas. Despite their usually large size, resection via laparoscopic approach is safe and effective. (Surgery 2011;149:99-105.)

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Neoplasms of ganglion cell origin include neuroblastomas, ganglioneuroblastomas, and ganglioneuromas, with descending degree of immaturity and malignant behavior. Ganglioneuromas arise most commonly from mediastinal and aortocaval sympathetic ganglia, and less frequently in the adrenals, and affect primarily pediatric patients and young adults.1-3 They may present de novo as primary neoplasms, but can also evolve from neuroblastomas either spontaneously or after response to treatment.3-6 Their reported incidence is less than 5% in series of adrenalectomies.7,13 The aim of this study is to delineate the clinical course, diagnostic imaging, and operative treatment of primary adrenal ganglioneuromas in adults.

MATERIALS AND METHODS

From 1991 to 2008, we operated on 150 adrenal incidentalomas. Seven patients (4.6%) were proven histologically to have primary adrenal ganglioneuromas (Table). They were 4 females and 3 males, with a mean age of 50 years (range, 39–64) and no medical history of neuroblastoma. Their clinical, diagnostic, and operative data were collected retrospectively. All 7 neoplasms were incidental, ultrasonographic findings during investigation of abdominal pain, blunt abdominal trauma, and breast cancer follow-up in 1 patient each, and routine check-up in the remaining 4. Except for the patient with abdominal pain and suspected gallstones, all ultrasonographies included upper and lower abdominal examination. Abdominal
computer tomography (CT) was done subsequently in all patients. Biochemical and hormonal screening was carried out in all patients to exclude functional cortical adenomas and pheochromocytomas. One patient had 131I-MIBG scanning due to a marginal increase in urinary levels of vanillylmandelic acid (VMA), and the patient with a history of breast cancer underwent an FDG-PET scan to differentiate an adrenal mass 5 cm in size. Indications for adrenalectomy included increased size in 4 patients, suspected metastasis in 1 patient, and pheochromocytoma in 2 patients. MEDLINE was used to review papers regarding “primary adrenal ganglioneuromas in adults.”

RESULTS

Clinical and hormonal findings. All but 2 patients were asymptomatic. As seen in the Table, patient 2 had complaints of atypical upper abdominal pain and a 10-cm adrenal mass was found during ultrasonographic investigation for suspected cholecystitis. Patient 3 presented with hypertensive episodes (systolic pressure, 200–220 mmHg) on grounds of poorly controlled arterial hypertension.

Hormonal evaluation disclosed 2 patients with mildly increased plasma concentrations of dopamine (134.9 pg/ml with normal upper limit <85 pg/ml, patient 3) and urine VMA (14.1 mg/24 hr with normal upper limit 12.6 mg/24, patient 5) respectively. The increased urinary VMA was found several days after the mild, blunt abdominal trauma in patient 3.

Imaging findings. Computed tomography: All neoplasms were reported as unilateral adrenal lesions and six of seven were right sided. Mean size was 6.8 cm (range, 4–13), while 4 were larger than 5 cm (Table). All cases had a solid appearance and low unenhanced attenuation value, up to 30 Hounsfield units (HU). Contrast enhanced CT showed increased attenuation of 60 HU in 1 (patient 6; Fig 1, A and B). Calcifications were evident in 2 neoplasms of 13 cm (patient 4; Fig 2) and 6 cm (patient 5). The remaining neoplasms were homogeneous. Neither CT showed evidence of surrounding tissue infiltration or regional lymph node enlargement.

Functional imaging: A 39-year-old male (patient 5) presented with a right-sided incidentaloma of 6 cm, which was discovered during imaging work up for blunt abdominal trauma. The patient was otherwise asymptomatic, and his 24-hr urine levels of VMA exceeded marginally the upper normal limit. Further evaluation with 131I-MIBG scintigraphy was undertaken, showing radioactive concentration corresponding to the right adrenal.

Patient 6 was a 43-year-old female with a history of bilateral lobular breast cancer. On follow-up 2 years postoperatively, a 5-cm right adrenal mass was discovered. The lesion was attributed to a metastasis and a PET-CT was done to verify diagnosis. 9.9 mCi 18F-FDG were administered, and 60 minutes later a double helical CT and PET were carried out. The tomography showed a right adrenal neoplasm with increased metabolic activity (SUVmax 4; Fig 3).

Treatment. All patients underwent uneventful complete resections, 3 open and 4 laparoscopic adrenalectomies. An open retroperitoneal approach was used in patient 1, while patients 2 and 4 underwent open, transabdominal adrenalectomy due to size (10 and 13 cm, respectively) and radiologic suspicion of malignancy. Mean operative time of open procedures was 102 min (range, 75–150).

Patients 3 and 5–7 underwent anterior laparoscopic adrenalectomy. All procedures were completed

<table>
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<tr>
<th>Patient #</th>
<th>Gender</th>
<th>Age</th>
<th>Symptoms</th>
<th>CT size (cm)</th>
<th>Pre contrast HU</th>
<th>Post contrast HU</th>
<th>Functional status</th>
<th>Preliminary diagnosis</th>
<th>Surgical technique</th>
<th>Histological size (cm)</th>
<th>Weight (g)</th>
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without conversion. Mean laparoscopic operative time was 136 min (range, 75–270).

We had no mortality and minor morbidity. Patient 3 developed pulmonary atelectasis of the right base. No patient required blood transfusion. Mean duration of hospitalization was 2.8 days (range, 2–5). There was no recurrence, during a mean follow-up of 6.4 years (range, 1–18). The abdominal pain of patient 2 and the hypertensive episodes of patient 3 were relieved after the adrenalectomy, although patient 3 is on antihypertensive medications to remain normotensive.

**Histopathology.** Mean tumor size on pathologic examination was 7.7 cm (range, 4–13) on maximum diameter, despite the mean radiologic preoperative size of 6.8 cm. The mean specimen weight was 268 g (range, 48–990). All neoplasms consisted of fascicles of Schwann-like cells and dispersed mature ganglion cells. No neoplasm showed immature neuroblastic cells or areas of pheochromocytoma. Two neoplasms showed calcifications. Although 6/7 neoplasms seemed macroscopically to compress adjacent yellow adrenal tissue, close microscopic observation of multiple sections revealed areas of entrapment of normal elements of the adrenal cortex within the neoplasm in all seven ganglioneuromas (Fig 4). In 1 patient, the neoplasm macroscopically seemed to arise within in the adrenal with destruction of the surrounding gland (Fig 5). These findings are strong indications that all neoplasms were primary adrenal ganglioneuromas. Immunohistochemistry was employed in patients 4–6, showing positive staining of ganglion cells for neuron-specific enolase (NSE; Fig 6), Synaptophysin, and positive staining of Schwann cells for S100 and CD57. Entrapped adrenal cortical cells were negative for the above mentioned markers and positive for Inhibin A.

**DISCUSSION**

Primary adrenal ganglioneuromas in adults are reported sporadically as case reports or in small series. We identified approximately 230 cases in the literature. Their most relevant clinical characteristics are those of hormonally inactive, slow growing, and incidentally discovered neoplasms, findings consistent with most of our patients (Table). Occasionally they may produce non-specific, mass-related symptoms, as in patient 2. Less common manifestations include catecholamine secretion, as was the case in our patient 3, VIP-related diarrhea, and virilization. Clinical, biochemical, and scintigraphic adrenergic activity mimicking pheochromocytomas is not uncommon in pediatric ganglioneuromas and neuroblastomas, but is found rarely to be evident in mature ganglioneuromas. Erem

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**Fig 1.** CT showing a right adrenal ganglioneuroma with (A) low unenhanced attenuation of 30 HU and (B) post-contrast enhancement of 60 HU.

**Fig 2.** Ganglioneuroma 13 cm in size with multiple calcifications, suspicious of adrenal carcinoma.
et al\textsuperscript{19} reported a patient with a 4-cm, dopamine-secretive adrenal ganglioneuroma in a 46-year-old woman with hypertensive crises, whereas Koch et al\textsuperscript{20} described symptomatic, fractionated metanephrines excess in a 63-year-old woman with concomitant VIP immunostaining of a 5-cm adrenal ganglioneuroma. Interestingly, a case of sudden death has been attributed to catecholamine hypersecretion of a 1-cm ganglioneuroma.\textsuperscript{21} Our patient with hypertensive episodes (patient 3) had a 5-cm ganglioneuroma, whereas larger neoplasms were metabolically inactive. Two of our patients (3 and 5) had borderline increases in blood and urine metanephrines, and were operated for a suspected pheochromocytoma (PCC). A less than 2-fold increase in blood and/or urine metanephrines is of low specificity regarding biochemical diagnosis of PCC,\textsuperscript{28} especially in patients with potential drug interactions.\textsuperscript{29} Both our patients were free of medications by the time their neoplasms were discovered. None of our patients exhibited any histologic components of a

\textbf{Fig 3.} \textsuperscript{18}F-FDG PET-CT shows increased tracer uptake of right adrenal lesion with a standardized uptake value (SUV\textsubscript{max}) of 4, suggestive of metastatic adrenal neoplasm (arrows).

\textbf{Fig 4.} Macroscopic appearance of adrenal ganglioneuroma (white) destroying the normal adrenal tissue (yellow).

\textbf{Fig 5.} Mixture of large ganglion cells (center and right, short arrows) and spindle-shaped Schwann like cells (center, long arrow). Entrapment of adrenal cortical cells (left, arrowhead) suggests primary adrenal ganglioneuroma. H&E \texttimes 400, original magnification.
pheochromocytoma. Less than 30 cases of a mixture of ganglioneuroma/pheochromocytoma have been reported; all were benign and, in addition to secreting catecholamines, several of these neoplasms also secreted neuropeptides of pancreatic islet cells. Occasionally, a mixture of histology of adrenal ganglioneuromas with cortical adenoma and myelolipoma has been described.

Imaging characteristics of adrenal ganglioneuromas on CT have been described as well circumscribed, low attenuated, homogeneous masses which demonstrate slight to moderate enhancement. Calcifications appear in about 50% of ganglioneuromas. The mean radiologic size in our patients was 6.8 cm, whereas the mean histologic size was 7.7 cm, underscoring again the radiologic underestimation of adrenal tumor size. Tumor size >5 cm, heterogeneity, and calcifications are considered radiologic signs suggestive of adrenal cancer. Because adrenal ganglioneuromas generally present as tumors >5 cm and frequently lack hormonal activity, they are usually treated as adrenal carcinomas. The largest neoplasms of our series measured 10 and 13 cm, respectively, the latter with discrete calcifications, and were treated by open, transabdominal adrenalectomy due to the suspicion of cancer.

One interesting finding of our study was the positive PET-CT in patient 6, who presented with a right adrenal mass proven to be a primary ganglioneuroma; the medical history, radiologic features, and macroscopic appearance were suggestive of an adrenal metastasis. A previously described incident of positive 131I MIBG uptake pertained to a patient with a history of treated neuroblastoma in adulthood. Whole body PET using 18FDG integrated with CT has been shown to be highly accurate in differentiating malignant adrenal masses. Nevertheless, although the negative predictive value approaches 100%, the specificity of the method was reported to be 90% in the largest study evaluating 94 adrenal masses in patients with lung cancer. PCCs in particular are found to accumulate FDG. Common neurogenic origin of PCCs and ganglioneuromas may have a pathophysiologic implication regarding FDG uptake in our patient.

Data regarding positive 131I MIBG uptake of adrenal ganglioneuromas in adults, as was the case in patient 5, are scarce and controversial regarding secretive profile. The few published reports have not shown any consistent correlation between positive scanning and functional status.

Prognosis of completely resected mature adrenal ganglioneuromas is excellent. We encountered no recurrence, and all adrenalectomies were carried out with no mortality and minimal morbidity despite the large size of the neoplasms. Complete resection of ganglioneuromas is not only feasible but also necessary, because malignant transformation has been reported. We believe that a laparoscopic approach should be used in almost all adrenal masses irrespective of the size, with the exception of the adrenal carcinoma infiltrating the surrounding tissues as seen on preoperative imaging. There is always the possibility to convert the laparoscopic procedure to an open adrenalectomy if needed. Similar “liberal” surgical attitudes are shared recently by most experienced endocrine surgeons.

REFERENCES


