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## Case Report

# Nonseminomatous Germ-Cell Tumor Presenting as Bilateral Adrenal Masses

Neelam Baral, MD<sup>1</sup>, Rashika Bansal, MD<sup>2,\*</sup>, Binaya Basyal, MD<sup>3</sup>, Wen Lee, MD<sup>4</sup>, Kanchan Kulkarni, MD<sup>5</sup>, Vitaly Kantorovich, MD<sup>6</sup>, Meeta Sharma, MD<sup>7</sup>

<sup>1</sup> Department of Endocrinology, Georgetown University, Washington, District of Columbia

<sup>2</sup> Department of Endocrinology, National Institutes of Health, Bethesda, Maryland

<sup>3</sup> Department of Cardiology, Georgetown University, Washington, District of Columbia

<sup>4</sup> Department of Pathology, Medstar Georgetown University, Washington, District of Columbia

<sup>5</sup> Department of Nuclear Medicine, Medstar Washington Hospital Center, Washington, District of Columbia

<sup>6</sup> Department of Endocrinology, Hartford Hospital, Hartford, Connecticut

<sup>7</sup> Department of Endocrinology, Medstar Washington Hospital Center, Washington, District of Columbia

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## ABSTRACT

**Objective:** Many tumors can metastasize to the adrenal glands, making the diagnosis of adrenal masses challenging. Awareness that rare primary tumors can metastasize to the adrenals and consideration of biopsy for their diagnosis, sometimes at extra-adrenal sites, is essential to prevent unnecessary adrenalectomies and facilitate the right treatment. We report a rare case of bilateral adrenal masses due to metastasis from a nonseminomatous germ-cell tumor of a retroperitoneal lymph node origin.

**Methods:** The diagnosis of the adrenal masses from the nonseminomatous germ-cell tumor of a retroperitoneal lymph node origin was based on a retroperitoneal lymph node core biopsy. An initial core biopsy of the adrenal gland revealed necrotic tissue and inflammatory cells without evidence of malignancy. Due to nondiagnostic findings, the core biopsy was repeated, which showed degenerating cells with a high mitotic index and immunohistochemical staining positive for vimentin, suggesting the possibility of a high-grade sarcoma. A retroperitoneal lymph node biopsy was performed. The patient was started on chemotherapy.

**Results:** A 34-year-old man presented with acute left upper-abdominal pain of 2 weeks and tenderness on the left upper quadrant of the abdomen, and he was found to have bilateral adrenal masses. Laboratory results showed the following: adrenocorticotropic hormone 41 pg/mL (7–69 pg/mL), metanephrine <0.1 nmol/L (0–0.49 nmol/L), normetanephrine 0.99 nmol/L (0–0.89 nmol/L), and morning cortisol 3.1 µg/dL after a 1-mg dexamethasone-suppression test. His dehydroepiandrosterone sulfate level was 62 µg/dL (120–520 µg/dL), and 17OH progesterone level was 36 ng/dL (<138 ng/dL); androstenedione and serum estradiol levels were normal. Laboratory tests for tumor markers revealed the following: testosterone 21 ng/dL (241–827 ng/dL), prostate-specific antigen 0.57 ng/mL (0–4 ng/mL), alpha-fetoprotein 1.9 IU/mL (0.6–6 IU/mL), and beta-human chorionic gonadotropin 134 mIU/mL (0–1 mIU/mL).

**Conclusion:** We report a rare case of rapidly progressing adrenal masses in a young man, found to have metastasized from nonseminomatous germ-cell tumors. Histopathologic confirmation of the metastatic tumor was done, which prevented unnecessary adrenalectomy. The patient received appropriate chemotherapy.

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**Abbreviations:** AFP, alpha-fetoprotein; β-HCG, beta-human chorionic gonadotropin; CT, computed tomography; HU, Hounsfield units; NSGCT, nonseminomatous germ-cell tumor; USG, ultrasound.

\* Address correspondence and reprint requests to Dr Rashika Bansal, Adult Endocrine Fellow, National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bldg 10 CRC, Rm 7C-432A, 10 Center Drive, Bethesda, MD 20892.

E-mail address: [rashika.bansal@gmail.com](mailto:rashika.bansal@gmail.com) (R. Bansal).

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## Introduction

Incidentally found adrenal adenomas have an overall prevalence of 4.4% when detected by computed tomography (CT), but the prevalence may be higher in elderly, obese, diabetic, and hypertensive patients.<sup>1</sup> Adrenal adenomas are functional in at least 30% to 50% of cases.<sup>2,3</sup> Size and imaging characteristics are the 2 major

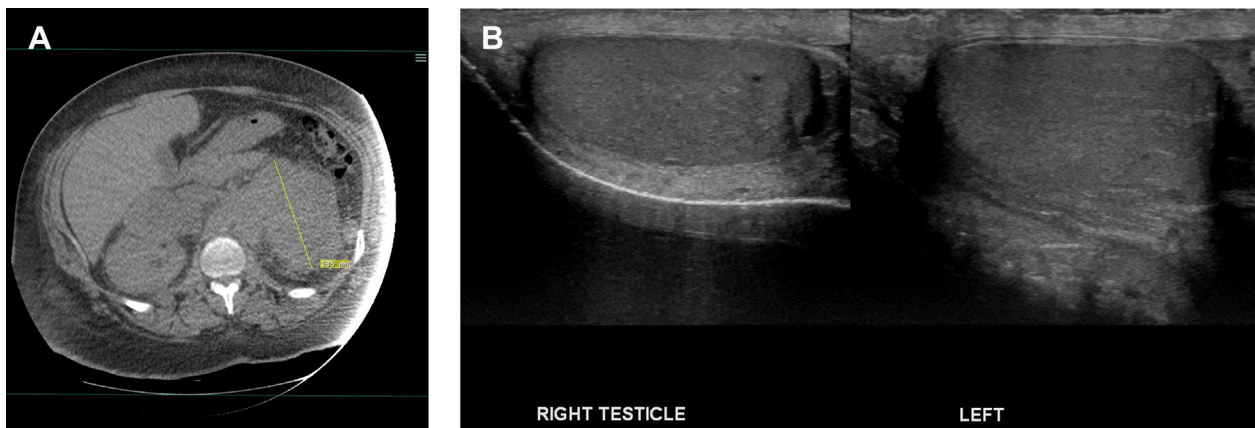


Fig. 1. H&E stained histology sections showing malignant cells (arrow).

predictors of differentiation of benign tumors from malignant tumors. Malignant adrenal masses are usually more than 4 cm in diameter, with a radiodensity of >10 Hounsfield units (HU) on unenhanced CT, reflecting low lipid content.<sup>4,5</sup> With delayed contrast-enhanced CT, benign adenomas typically exhibit a rapid washout, whereas malignant adrenal masses show a delayed contrast washout (<50% 10 minutes after the administration of the contrast.<sup>6</sup>

Bilateral adrenal masses can result from metastatic disease, congenital adrenal hyperplasia, bilateral cortical adenomas, and infiltrative disease of the adrenal glands.<sup>7</sup> At the time of detection of metastatic adrenal masses, the primary cancer has usually already been identified, and metastasis to the adrenal glands without a known primary cancer is very rare.<sup>8</sup> The primary role of fine needle aspiration biopsy is to differentiate adrenal and non-adrenal tissues, but the possibility of a pheochromocytoma should always be excluded by biochemical testing prior to a fine needle aspiration biopsy.<sup>9</sup> We report a rare case of bilateral adrenal masses due to metastasis from a nonseminomatous germ-cell tumor (NSGCT), which posed diagnostic challenges because of lack of evidence of a primary tumor.

**Case Report**

A 34-year-old African American man with a past medical history of hypertension and heart failure presented with abdominal pain of 2 weeks. A CT scan of the abdomen without contrast showed bilateral adrenal masses and retroperitoneal lymphadenopathy. The left adrenal gland was lobulated, heterogeneously enhancing, and measured 11 × 9 × 5 cm. The right adrenal gland was also enlarged to 6.5 × 3.4 × 7.7 cm, with an unenhanced CT attenuation of 10 HU. Multiple enlarged and centrally necrotic retroperitoneal lymph nodes (maximum diameter 5.4 cm) were present along with iliac and inguinal lymphadenopathy (Fig. 1 A). Laboratory testing was performed (Table 1). AM cortisol level after 1-mg dexamethasone at midnight was 3.1 µg/dL. Adrenocorticotropic hormone stimulation test was consistent with adrenal insufficiency, with a repeat baseline cortisol level of 8.7 µg/dL and stimulated cortisol level of 11.2 µg/dL at 60 minutes. The patient was treated with 20 mg of hydrocortisone in the morning and 10 mg in the afternoon. Plasma renin and aldosterone levels were not assayed as potassium level was normal. Additional laboratory tests revealed an adrenocorticotropic hormone level of 41 pg/mL (7-69 pg/mL), metanephrine level of <0.1 nmol/L (0-0.49 nmol/L), and normetanephrine level of 0.99 (0-0.89 nmol/L). A complete blood count showed eosinophilia (8.8%). Flow cytometry of the peripheral

**Table 1**

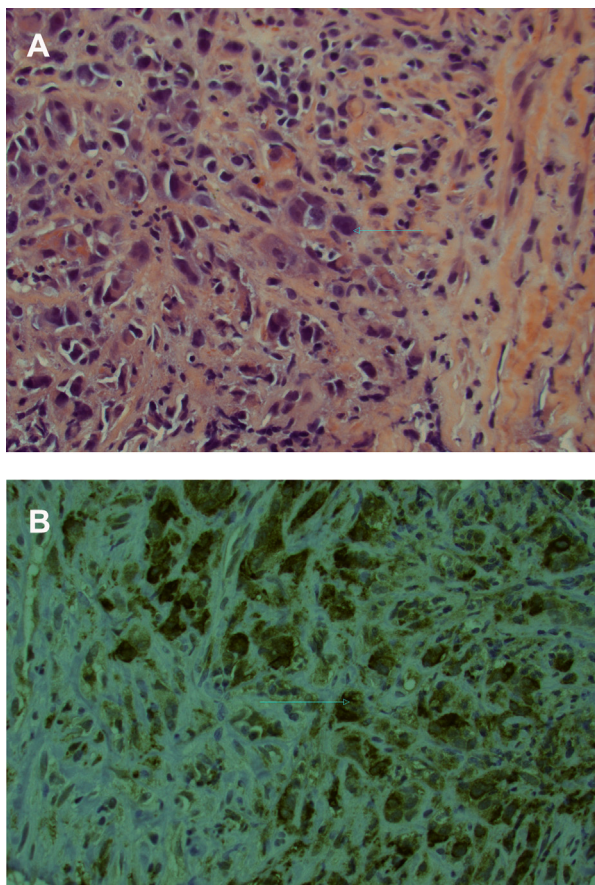
Biochemical Testing

Parameter	Laboratory result	Normal range
ACTH (pg/mL)	41	7-69
Metanephrines (nmol/L)	<0.1	0-0.49
Normetanephrines (nmol/L)	0.99	0-0.89
DHEAS (µg/dL)	62	120-520
17OH progesterone (ng/dL)	36	<138
Testosterone level (ng/dL)	21	241-827
PSA (ng/mL)	0.57	0-4
AFP (IU/mL)	1.9	0-6.6
β-HCG (mIU/mL)	134	0-1

Abbreviations: ACTH = adrenocorticotropic hormone; AFP = alpha-fetoprotein; β-HCG = beta-human chorionic gonadotropin; DHEAS = dehydroepiandrosterone sulfate; PSA = prostate-specific antigen.

blood did not show any immunophenotypic evidence of a monoclonal population of B cells, T cells, or blasts. Lactate dehydrogenase and creatinine kinase levels were normal. Total protein level was 9 to 10 mg/dL (6.3-8.2 mg/dL), and albumin level was 2 mg/dL (3.5-5 mg/dL), but serum and urine protein electrophoresis did not reveal an M spike. The patient underwent a core biopsy of the left adrenal mass, which predominantly revealed necrotic tissue and acute inflammatory cells with histiocytes and rare atypical cells without the evidence of malignancy. It was also negative for the presence of fungal organisms and acid-fast bacilli. Staining results for acid-fast bacilli, histoplasma, aspergillus, and cryptococcus were negative. Dehydroepiandrosterone sulfate level was 62 µg/dL (120-520 µg/dL), 17OH progesterone level was 36 ng/dL (<138 ng/dL), and androstenedione and serum estradiol levels were normal. Laboratory tests for tumor markers revealed a testosterone level of 21 ng/dL (241-827 ng/dL), prostate-specific antigen level of 0.57 ng/mL (0-4 ng/mL), alpha-fetoprotein (AFP) level of 1.9 IU/mL (0.6-6 IU/mL), and a beta-human chorionic gonadotropin (β-HCG) level of 134 mIU/mL (0-1 mIU/mL). Chest CT showed a subcentimeter mediastinal lymph node without pulmonary nodules, and brain magnetic resonance imaging result was normal. Scrotal ultrasound (USG) revealed punctate echogenic foci in both the right and left testicle, suggestive of microlithiasis but not definitive malignancy (Fig. 1 B).

A core biopsy of the left adrenal mass was repeated, which revealed malignant neoplasm. It contained necrotic tissue, degenerating tumor cells with enlarged hyperchromatic nuclei, prominent nucleoli, and frequent mitotic figures. The Ki-67 index was approximately 40%. Immunohistochemical staining was positive for vimentin, suggesting the possibility of a high-grade sarcoma but without a definitive diagnosis. Congo red, Gomori



**Fig. 2.** Immunohistochemical staining of tumor cells by  $\beta$ -HCG.  $\beta$ -HCG = Beta-human chorionic gonadotropin.

methenamine-silver, periodic acid-Schiff, and acid-fast bacilli staining results were negative. Because of the suspicion of metastatic disease, a core biopsy of the retroperitoneal lymph node was done, which revealed an NSGCT (Fig. 2 A and B). A retroperitoneal primary NSGCT with metastasis to the adrenal glands was the most likely diagnosis, with visceral metastasis and stage III (pTx N3 M1 S1) disease. The patient had a poor response to a chemotherapy regimen of bleomycin, etoposide, and cisplatin and passed away within 5 months of the diagnosis.

## Discussion

Adrenal incidentalomas are commonly unilateral but can present as bilateral masses in 18% of cases.<sup>10</sup> Biochemical testing is required to rule out pheochromocytoma, which requires an extensive workup (Table 2). Here, we describe a previously unreported case of markedly enlarged bilateral adrenal masses due to metastatic NSGCT. In a series of 7 patients diagnosed with primary adrenal insufficiency due to bilateral adrenal disease, the common diagnoses were metastases (lung and breast adenocarcinoma), diffuse large B-cell lymphoma, tuberculosis, cryptococcosis, histoplasmosis, and Erdheim-Chester disease.<sup>11</sup> Histoplasmosis, paracoccidioidomycosis, sarcoidosis, and amyloidosis are the most common fungal infections to infiltrate the adrenal glands, and in endemic countries, tuberculosis can present as an adrenal mass. Fungal adrenal involvement manifests radiographically as a glandular enlargement with peripheral enhancement, contour preservation, and calcifications.

**Table 2**  
Differential Diagnosis of Bilateral Adrenal Mass

Metastatic disease
Lymphoma
Cortical adenoma
Fungal infection
Mycobacterial infection
Corticotropin-dependent Cushing syndrome
Pheochromocytoma
Primary aldosteronism
Sarcoidosis
Infiltrative disease—amyloidosis

Adrenal masses are rare, presenting the symptoms of malignancy, with diagnostic challenges. A study by Young et al<sup>12</sup> showed a 4.7% prevalence of adrenocortical carcinoma and 2.5% prevalence of metastatic cancer among 2005 patients with adrenal incidentaloma. In a study of large adrenal tumors, older age at diagnosis, male sex, nonincidental mode of discovery, larger tumor size, and high unenhanced CT attenuation were found to be significant predictors of malignancy using a multivariate analysis.<sup>13</sup> Tumor size is the most important risk factor, with malignancy being 8 times more common in masses larger than 4 cm.<sup>14</sup> Moreover, using a cutoff of >10 HU, noncontrast CT has a high sensitivity (100%, 95% confidence interval: 91%–100%) but poor specificity for detecting malignancy. The positive predictive value for the detection of malignancy is 70% to 80%, suggesting that few tumors with a density of >10 HU are likely to be benign.<sup>15</sup> Other predictors include irregular shape, heterogenous content, necrosis, size greater than 4 cm, >10 HU, rapid rate of growth along with generalized symptoms of weight loss, malaise, and cachexia.<sup>4</sup> In a series of patients referred for suspected unknown primary cancer, metastatic cancer presenting as a true adrenal incidentaloma was found to be extremely rare, and biopsy was helpful only in cases with a known history of malignancy, symptoms, or radiographic evidence of malignancy.<sup>8</sup>

The current guidelines recommend the consideration of adrenal biopsy in patients at a high risk of adrenal malignancy not originating from the adrenal cortex and in cases with suspected infiltrative or infectious processes.<sup>16</sup> Adrenal biopsy is an invasive procedure, with a potential nondiagnostic rate of up to 4.4% to 8.7%.<sup>17</sup> It is 87% sensitive and 96% specific in the overall diagnosis of malignancy when the nondiagnostic rates are not accounted for.<sup>16</sup> The diagnosis of malignancy was missed in the first adrenal core biopsy as the sample predominantly contained necrotic tissue. A high index of suspicion should be maintained in cases with non-diagnostic biopsy results if the imaging characteristics suggest malignancy. The most common source of adrenal metastasis is the lung (51%), followed by the kidney, colon, breast, esophagus, pancreas, liver, and stomach.<sup>18</sup> Adrenal metastasis of genitourinary primary tumors has been demonstrated to have the highest prevalence of bilateral disease.<sup>19</sup> In our case, the patient had bilateral adrenal metastasis from an extragonadal germ-cell tumor; hence, locating the primary tumor was challenging.

Germ-cell tumors are the most common solid tumors in men between 15 and 34 years of age.<sup>20</sup> They commonly arise in the testes, and when germ-cell tumors are present in extragonadal sites, testicular USG is necessary to rule out primary testicular tumor. Retrospective studies have shown an association between testicular microlithiasis, calcification, and testicular tumors as these areas represent “burned-out” tumors. However most of these studies are cross-sectional,<sup>21–23</sup> and the relationship between testicular microlithiasis and testicular cancer is still controversial.<sup>24,25</sup> Fewer than 10% of germ-cell tumors arise from extragonadal primary sites, with the mediastinum and retroperitoneum being the most common. In the case presented, testicular USG did

not show definitive malignancy but showed testicular microlithiasis, and the retroperitoneal lymph node biopsy showed a nonseminomatous germ-cell tumor, thus confirming the diagnosis of NSGCT of a retroperitoneal lymph node origin.

NSGCT can be of various types—embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac carcinoma. Measurement of tumor markers, biopsy, immunohistochemical studies, and determining the degree of elevation of tumor markers is helpful in assessing prognosis. The  $\beta$ -HCG and AFP levels are modestly elevated in embryonal carcinoma, but they can also be normal. The  $\beta$ -HCG level is markedly elevated in choriocarcinoma, and the AFP level is elevated in yolk sac tumors. Our patient had a normal AFP level and an elevated  $\beta$ -HCG level, and the testicular USG was not suggestive of malignancy, highlighting the crucial step of obtaining biopsies of mediastinal lymph nodes for the final diagnosis.

Retroperitoneal NSGCT often has a poor outcome because of an advanced presentation. A  $\beta$ -HCG level of  $>50\,000$  mIU/mL and an AFP level of  $>10\,000$  ng/mL are predictive of poor prognosis in choriocarcinoma and yolk sac tumors, respectively. Chemotherapy is initially used in patients with stage III NSGCT or stage II disease with multifocal retroperitoneal lymph node involvement, lymph nodes more than 3 cm in diameter, or tumor-related back pain. Combination chemotherapy results in complete remission in 70% to 80% of patients, with remission rates in NSGCT of a testicular origin being higher (79%) than those of similar tumors of an extragonadal origin (60%).<sup>26</sup>

## Conclusion

Metastasis to the adrenal glands is an uncommon manifestation of germ-cell tumors and can be challenging to diagnose when the location of the primary tumor is extragonadal. Rapidly enlarging adrenal masses in a young man should prompt the consideration of metastatic germ-cell tumors as a possible differential to avoid unnecessary adrenalectomy and determine the appropriate chemotherapeutic regimen. Such patients should be treated by a multidisciplinary team including experts in endocrinology, endocrine surgery, oncology, and pathology.

## Disclosure

The authors have no multiplicity of interest to disclose.

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