Adrenal insufficiency as presenting feature of non-Hodgkin lymphoma

Bruce L. Jacobs, MD,[1] Todd M. Blodgett, MD,[2] Sara E. Monaco, MD,[3] Ronald L. Hrebinko Jr, MD,[1] Samuel A. Jacobs, MD[4]

[1]Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[2]Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[3]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[4]Department of Hematology Oncology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

JACOBS BL, BLODGETT TM, MONACO SE, HREBINKO RL, JACOBS SA. Adrenal insufficiency as presenting feature of non-Hodgkin lymphoma. The Canadian Journal of Urology. 2010;17(5):5411-5414.

Lymphomatous involvement of an adrenal gland during the course of a lymphoma is common, but a primary presentation of adrenal insufficiency in a patient with lymphoma involving both adrenal glands is rare. We describe a 36-year-old man with non-Hodgkin lymphoma (NHL) who presented with adrenal insufficiency. His evaluation consisted of several imaging modalities, including positron emission tomography-computed tomography (PET-CT) scans, which were helpful in defining the extent of disease prior to treatment and in monitoring the patient's response to treatment. Our case illustrates the importance of preoperative evaluation to exclude a lymphoma, particularly in patients with bilateral renal and/or adrenal masses.

Key Words: adrenal insufficiency, non-Hodgkin lymphoma, PET-CT

Case

A 36-year-old previously healthy male presented with new onset malaise, asthenia, and depression. He denied any pain, fevers, or night sweats and initial laboratory studies were within normal limits. Several months went by without improvement and were marked by a 50 pound weight loss, difficulty sleeping, and lassitude. In desperation, he went to an emergency room for depression. He appeared cachectic, but was alert and oriented. He was afebrile with stable vital signs. Pertinent physical exam findings included no jaundice, palpable adenopathy, or organomegaly. Initial laboratory studies included the following: sodium 110 mMol/L (136-146), potassium 6.6 mMol/L (3.5-5.0), chloride 74 mMol/L (98-107), bicarbonate 21 mMol/L (21-31), BUN 29 mg/dL (8-26), creatinine 1.5 mg/dL (0.5-1.4), bilirubin 1.7 mg/dL (0.3-1.5), and transaminases and blood counts were within normal limits. An abdominal ultrasound, which was obtained to further evaluate his elevated bilirubin, incidentally identified bilateral renal masses. A subsequent contrasted computed tomography (CT) scan revealed a large upper pole right renal mass as well as a large left renal mass that appeared to involve the left adrenal gland but without retroperitoneal adenopathy.

The patient was admitted and evaluation of his adrenal function included normal ACTH 14 pg/mL (9-46) and aldosterone < 2.0 ng/dL (0-21) levels. A cosyntropin stimulation study showed a baseline cortisol level of 3.82 µg/dL, a 30-minute level of 8.06 µg/dL, a 60-minute level of 12.3 µg/dL, and a 90-minute level of 13.8 µg/dL. A normal stimulated cortisol level should be 18 to 20 µg/dl or greater. The patient was treated with hydrocortisone and fludrocortisone and his electrolytes and renal function normalized within a few days.

Accepted for publication July 2010

Address correspondence to Dr. Bruce L. Jacobs, Department of Urology, University of Pittsburgh School of Medicine, 3471 Fifth Avenue, Suite 700, Pittsburgh, PA 15213-3232 USA

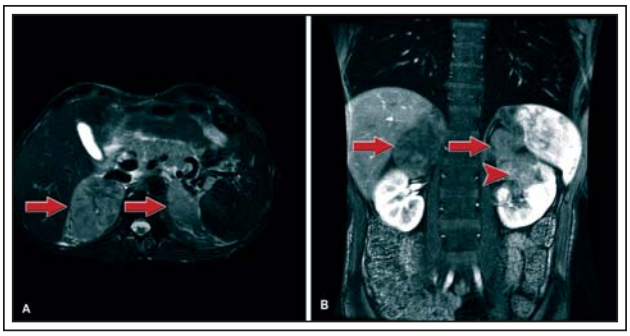

Figure 1. Axial T2 weighted image (a) shows bilateral adrenal masses (arrows) with heterogeneous signal. (b) Post contrast image shows some mild patchy enhancement (arrows) with left renal invasion (arrowhead).

A magnetic resonance image (MRI) of the abdomen with and without contrast showed bilateral necrotic adrenal masses, Figure 1a. The left adrenal mass extended into the left kidney and the right kidney appeared normal. An ultrasound guided fine needle aspiration (FNA) biopsy of the left adrenal was performed, and the results were consistent with a high-grade B-cell non-Hodgkin lymphoma (NHL) of non-germinal center type with a high Ki67 proliferation index and necrosis, Figure 2. Fluorescence in situ hybridization (FISH) studies for the *MYC* gene rearrangement were performed and excluded the possibility of a Burkitt lymphoma. Additional work up with a fluorodeoxyglucose F 18 (FDG) positron emission tomography (PET)-CT scan, Figure 1b, showed enlarged, FDG-positive nodes in the neck, para-aortic, mesenteric, iliac and right inguinal regions, as well as the large adrenal masses.

The patient was treated with a chemotherapy regimen developed for aggressive, high risk lymphomas known as the "Vanderbilt" regimen, and, after completion of this regimen, his PET-CT normalized with atrophic appearing remnants of the adrenal glands, Figure 3. The patient remains disease-free 2 years after diagnosis. However, he will require life-long steroid replacement therapy since post-treatment evaluation of his adrenal-pituitary axis failed to show an adrenal response to ACTH stimulation.

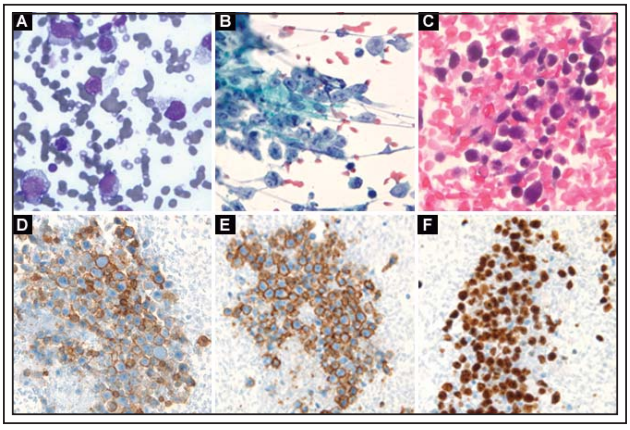

Figure 2. Cytomorphologic features of malignant B-cell lymphoma. The aspirate smears revealed dyscohesive malignant cells with large nuclei and variable amounts of dense basophilic cytoplasm with occasional vacuoles, in a background of lymphoglandular bodies. (a. Diff-Quik stain, original magnification X600). The coarse chromatin and prominent irregular nucleoli are seen best on the alcohol-fixed smears (b. Papanicolaou stain, original magnification X400). The cell-block sections showed the dyscohesive large tumor cells (c. Hematoxylin & eosin stain, original magnification X400), which were positive for leukocyte common antigen/LCA (d. original magnification X400) and CD20 (e. original magnification X400). There was also a high proliferation index with at least 90% of tumor cells showing positivity for Ki67 (f. original magnification X400). Not shown is a MUM-1 immunohistochemical stain which was positive, indicating that this lymphoma was most likely of non-germinal center type.[13]

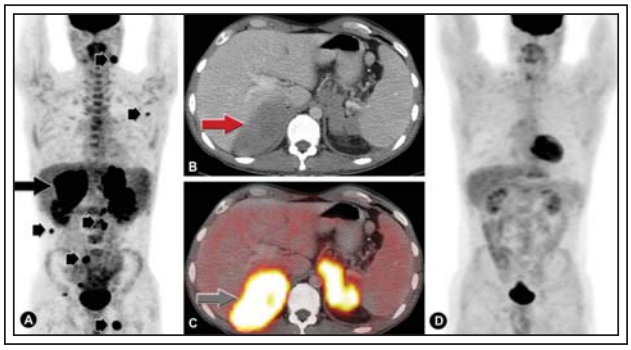

Figure 3. Coronal PET MIP image (a) shows the adrenal masses (long arrow) with intense FDG activity. Also note multiple small hypermetabolic lesions (short arrows) corresponding to additional malignant lesions, mostly lymph nodes, not identified on the MRI. Corresponding axial contrast enhanced CT (b) and axial fused PET/CT (c) shows the adrenal masses to be hypoattenuating with mild enhancement. Post treatment scan (d) shows complete metabolic response with resolution of abnormal metabolic activity within all of the previously identified lesions.

Discussion

Lymphomatous involvement of the adrenal gland may occur in as many as 25% of patients with NHL in autopsy studies.[1,2] With the current sophisticated imaging techniques, the incidence of adrenal involvement is likely even higher. It is rare, however, for a patient with lymphoma to present with symptomatic adrenal insufficiency as a primary presentation.[1] The overall prognosis in early series was poor with few patients achieving a complete durable response.[3,4] However, therapy was not well characterized and included surgery, combination chemotherapy and radiation. In many instances, the therapy used would be considered less than optimal by today's standards.

An important feature of the medical oncology evaluation was obtaining a PET-CT scan, which showed more extensive disease including 18-FDG-avid lymph nodes in the cervical chain, para-aortic, iliac, mesenteric, and right inguinal regions. Given that the patient was diagnosed with NHL and that there was extra-adrenal/renal disease, surgery was not an option for disease control. This case demonstrates the added staging information gained from a baseline PET-CT scan. Moreover, a post-treatment PET-CT scan was used to monitor the therapeutic response and, in some instances, may be used to predict outcome.[5-7]

While PET-CT scanning is routine for medical and surgical oncologists, it is less often used to evaluate extent of disease by urologists. Lymphoma is seldom the presenting diagnosis to the urologist and, in general, PET-CT is used much less often for evaluating primary urologic tumors in large part due to the urinary excretion of many PET tracers and the variable uptake in some urological tumors.[8] The 18-FDG detects increased glycolytic activity in neoplastic cells with a high metabolic rate and has increased uptake on PET imaging.[9] Using a PET-CT device allows the localization of functional findings detected on PET in anatomic structures shown on CT during one imaging procedure.[8] The use of 18-FDG PET-CT in renal cell carcinoma (RCC) is limited by its low sensitivity; this may be due to the increased background activity of healthy renal tissue and normal FDG excretion in urine.[10] In RCC, PET-CT may have a more active role in postoperative surveillance, with the advantages of covering the whole body in one procedure and no risk of additional renal toxicity from contrast.[11] In bladder cancer, Drieskens et al evaluated the use of 18-FDG PET-CT scans preoperatively in 55 patients to help diagnose metastatic disease and found the sensitivity, specificity, positive-predictive value, and negative-predictive value of 18-FDG PET-CT to be 60%, 88%, 75%, and 79%, respectively.[12] Newer agents such as ^{11}C Methionine and choline are not excreted in urine and may be utilized more frequently in PET imaging of bladder cancer in the future.[9]

Our case is of interest in that the prodrome of adrenal insufficiency began approximately 3 months before diagnosis. Once the diagnosis of adrenal insufficiency was made and it was apparent that large volume disease involved the adrenal glands and at least one kidney, an MRI was obtained to better delineate the lesions for operative planning. "Primary" adrenal lymphoma was considered in the differential diagnosis and thus, an FNA biopsy was performed in order to establish a diagnosis upon which to base therapy and avoid an unnecessary operation. This case exemplifies how a preoperative minimally-invasive biopsy, like an FNA, can be particularly advantageous in the setting of bilateral renal and/or adrenal masses to exclude the possibility of a lymphoma and, therefore, prevent unnecessary surgery. In addition, this case highlights how PET-CT can be advantageous prior to therapy in order to delineate the extent of disease and, in the post-therapy evaluation, monitor the therapeutic response to treatment. □

References

1. Rosenberg SA, Diamond HD, Jaslowitz B, Craver LF. Lymphosarcoma: a review of 1269 cases. *Medicine (Baltimore)* 1961; 40:31-84.
2. Straus DJ, Filippa DA, Lieberman PH, Koziner B, Thaler HT, Clarkson BD. The non-Hodgkin's lymphomas. I. A retrospective clinical and pathologic analysis of 499 cases diagnosed between 1958 and 1969. *Cancer* 1983;51(1):101-109.
3. Wang J, Sun NC, Renslo R et al. Clinically silent primary adrenal lymphoma: a case report and review of the literature. *Am J Hematol* 1998;58(2):130-136.
4. Ohsawa M, Tomita Y, Hashimoto M, Yasunaga Y, Kanno H, Aozasa K. Malignant lymphoma of the adrenal gland: its possible correlation with the Epstein-Barr virus. *Mod Pathol* 1996; 9(5):534-543.
5. Juweid ME, Wiseman GA, Vose JM et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 2005;23(21):4652-4661.
6. Haioun C, Itti E, Rahmouni A et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. *Blood* 2005;106(4):1376-1381.
7. Hutchings M, Loft A, Hansen M et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood* 2006;107(1):52-59.
8. Bouchelouche K, Oehr P. Positron emission tomography and positron emission tomography/computerized tomography of urological malignancies: an update review. *J Urol* 2008;179(1): 34-45.

9. Saksena MA, Dahl DM, Harisinghani MG. New imaging modalities in bladder cancer. *World J Urol* 2006;24(5):473-480.
10. Kang DE, White RL Jr, Zuger JH, Sasser HC, Teigland CM. Clinical use of fluorodeoxyglucose F 18 positron emission tomography for detection of renal cell carcinoma. *J Urol* 2004; 171(5):1806-1809.
11. Park JW, Jo MK, Lee HM. Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. *BJU Int* 2009;103(5):615-619.
12. Drieskens O, Oyen R, Van Poppel H, Vankan Y, Flamen P, Mortelmans L. FDG-PET for preoperative staging of bladder cancer. *Eur J Nucl Med Mol Imaging* 2005;32(12):1412-1417.
13. Hans CP, Weisenburger DD, Greiner TC et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004; 103(1):275-282.

EDITORIAL COMMENT

Lymphomatous involvement of the adrenal is not uncommon. However, adrenal insufficiency as a result of this involvement is rare. This serious occurrence can occur with extensive bilateral involvement with metastatic disease or occasionally from involvement of a solitary functioning adrenal. This may also occur if the contralateral adrenal was destroyed by adrenal hemorrhage especially in patients with metastatic disease or bleeding diathesis.

Nabil K. Bissada, MD
Department of Urology
Central Arkansas Healthcare Systems
Little Rock, Arkansas
USA