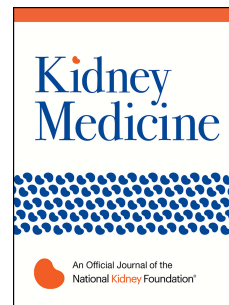


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Lymphoma and the Kidney: A Kidney Biopsy Teaching Case

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ABSTRACT

Lymphomatous infiltration of kidney parenchyma is a frequent complication of systemic hematological malignancies, and often shows subtle clinical presentation. Diffuse large B-cell lymphoma (DLBCL) represents the most frequent form involving the kidney, with advanced stage at the diagnosis, poor outcome and risk of central nervous system relapse if not adequately treated. Kidney biopsy can provide a specific and early detection of these cases, helping in the differential diagnosis with more frequent entities. Finally, further hematological work-up (bone marrow biopsy, complete blood cell count, positron emission tomography scan) can distinguish secondary involvement of the kidney from the rarer kidney-limited forms, especially in patients without a previous diagnosis of lymphoma. Making a prompt and correct diagnosis directs the management of these cases, and may improve the outcome, as described in the present report.

KEYWORDS

Kidney pathology; hematopathology; kidney limited lymphoma; DLBCL; kidney biopsy

Introduction

Lymphomatous infiltration of kidney parenchyma is a frequent complication of hematological disorders, present in around 34% of lymphoma patients in a large series¹. However, only 14% of cases are detected before death¹, and this under-diagnosis could be due to the subtle clinical presentation of kidney involvement, with only 0.5% of such cases showing acute kidney injury². Few data are available regarding the incidence of kidney infiltration for the different lymphoma subtypes. Diffuse large B-cell lymphoma (DLBCL) is the most frequent involving the kidney, showing advanced stage at diagnosis, poor outcome and risk of central nervous system relapse if not promptly detected and adequately treated³. Although the detection of parenchymal swelling/enlargement on imaging can be of help, kidney biopsy is mandatory in these cases, particularly in patients with no prior lymphoma diagnosis⁴. Finally, hematological work-up with appropriate staging (bone marrow biopsy, complete blood cell count, positron emission tomography [PET] scan) can allow the distinction of secondary kidney involvement in systemic disease from the rarer primary kidney lymphoma, especially in patients without previous history of hematological disease⁵. This can direct the management of these cases and may improve their outcome. Here we report a case of systemic DLBCL presenting with apparent initial kidney-limited involvement where diagnosis of the kidney component led to thorough clinical and radiographic staging that identified the full extent of disease, with discussion of the possible interpretative pitfalls in the histological assessment.

Case Report

A white man in his 50s with previous history of hypertension, coronary artery disease and obesity was referred to nephrology for evaluation of acute kidney injury in the setting of nausea, vomiting, and abdominal pain.

Initial Laboratory Data

Laboratory data showed serum creatinine 5.5 mg/dl, estimated glomerular filtration rate (eGFR) 11 ml/min/1.73m², urine protein/creatinine ratio 0.98, no hematuria and blood pressure 164/112 mmHg. Kidney ultrasound and chest-abdominal-pelvis CT scan showed mild enlargement of the kidneys (13.3 cm on the right and 12.5 cm on the left) without other significant findings. Since the clinical work-up failed to determine a possible cause of the sudden loss of kidney function, a percutaneous kidney biopsy was performed.

Kidney Biopsy

Kidney biopsy showed 4 glomeruli which were unremarkable. Immunofluorescence and electron microscopy showed no deposits. Kidney parenchyma was obliterated by an extensive mixed lymphoid infiltrate composed of small cells, spindled cells and a predominance of large lymphoid cells with abnormal nuclei (Figure 1A). The infiltrating cells were diffusely positive for B-cell markers CD20 (Figure 1B), PAX5, and CD79a, characteristic of a large B-cell lymphoma. There was also positivity for Bcl6 (Figure 1C) and negativity for CD10 and MUM1, indicating germinal center phenotype by the Hans classification⁶. The Ki-67 proliferative rate was 70-80% (Figure 1D). The abnormal cells were negative for EBER ISH, BCL2, c-Myc (<40%), CD138, CD30, CD3 and CD68 (markers of possible viral status, differentiation and grade, as

discussed below). Since c-Myc and BCL2 were negative, fluorescence in situ hybridization (FISH) for the detection of rearrangements of these loci has not been performed. There were scattered background CD3 and CD68 positive cells.

Diagnosis

Taken together, these findings were consistent with diffuse large B-cell lymphoma, NOS, although a large-cell transformation of an underlying systemic B-cell neoplasm could not be fully excluded.

After the preliminary kidney biopsy results, a repeat chest-abdominal-pelvis CT scan demonstrated unchanged bilateral kidney prominence without additional findings. Neck CT scan showed mildly enlarged tissue adherent to the inferior aspect of both parotid glands, measuring 1.1 x 1.7 cm on the right and 1.2 x 1.8 cm on the left, attributable to abnormal lymph nodes. The patient underwent subsequent hematological work-up with unremarkable complete blood cell count (white blood cell count $8.2 \times 10^3/\mu\text{L}$, red blood cell count $3.93 \times 10^6/\mu\text{L}$, hemoglobin 11 g/dl, hematocrit 32.3%, platelets $211 \times 10^3/\mu\text{L}$, neutrophils $6.13 \times 10^3/\mu\text{L}$, lymphocytes $1 \times 10^3/\mu\text{L}$, monocytes $1 \times 10^3/\mu\text{L}$, eosinophils $0.02 \times 10^3/\mu\text{L}$ and basophils $0.01 \times 10^3/\mu\text{L}$). A trephine bone marrow biopsy demonstrated no evidence of bone marrow involvement by lymphoma, further suggesting a possible form of kidney limited lymphoma. PET scan done after kidney biopsy report, however, demonstrated bilateral intraparotid positivity (proved to be benign Warthin tumor by biopsy) and systemic PET positivity in different sites (kidneys and adrenal glands bilaterally, thyroid gland, spleen and throughout the entire skeleton), ascribed to systemic involvement by the patient's lymphoma.

Clinical Follow-up

He was treated with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for his lymphoma. The patient required dialysis for 2 months. After 6 cycles of chemotherapy, PET scan showed a complete response with regression in all sites and the patient experienced an improvement of kidney function, with serum creatinine 2.2 mg/dl and eGFR 32 ml/min/1.73 m².

Discussion

The diagnosis of kidney lymphoma can be challenging due to the subtle clinical presentation, ranging from silent kidney masses that can mimic renal cell carcinoma, kidney abscesses or other kidney tumor metastasis by imaging studies, less frequently presenting with acute kidney injury or sub-nephrotic proteinuria, often lacking weight loss or flank pain⁷. This can lead to diagnostic delay and increased risk of poor outcome of these cases. In some series DLBCL represents the most frequent form of lymphoma involving the kidney, with bilateral forms accounting for 44% of cases³. Kidney biopsy typically shows extensive or complete obliteration of the parenchyma (Box 1), a shared feature of both reactive and neoplastic processes affecting the kidney. Several conditions can cause infiltrates of lymphoid cells in the kidney, but do not cause obliteration of kidney architecture. Acute interstitial nephritis is characterized by a polymorphic leukocytic interstitial infiltrate composed of B and T lymphocytes, plasma cells, macrophages, and even neutrophils associated with edema and tubulitis. Acute pyelonephritis can cause kidney swelling, and shows patchy inflammation with lymphocytes, plasma cells, and neutrophils with the presence of “neutrophilic plugs” in the tubular lumina. Malakoplakia and xanthogranulomatous pyelonephritis (XGP) are chronic inflammatory conditions caused by repeated infections and characterized by

diffuse and destructive histiocytic infiltrates, with CD68 positivity of these infiltrating cells. In malakoplakia, there are typical Michaelis-Gutmann bodies (concentric basophilic inclusions representing mineralized phagosomes composed of iron and calcium deposits), whereas XGP shows numerous foam cells. Finally, systemic inflammatory conditions, such as IgG4-related disease, can rarely involve the kidney and present with unilateral or bilateral masses. Biopsy shows a dense “storiform” fibrosis, an increased IgG4+ plasma cell infiltrate and frequently associated granular tubular basement membrane deposits.

Among the neoplastic processes, systemic hematological disorders can lead to diffuse infiltration of kidney parenchyma. The most frequent forms are represented by lymphomas (both low-grade B-cell non-Hodgkin and diffuse large B-cell lymphomas), followed by acute lymphoblastic leukemia and, rarely, myeloid neoplasms (such as acute myeloid leukemia and Langerhans and non-Langerhans histiocytosis)^{8,9}. All these are characterized by the presence of monotypic neoplastic elements and the employment of adequate immunohistochemical stains can aid in the differential diagnosis. EBV-positive DLBCL is characterized by in situ hybridization positivity for EBER in the neoplastic cells¹⁰, whereas plasmablastic lymphoma shows typical CD138 positivity¹¹. In anaplastic lymphoma (both ALK positive and negative forms) neoplastic elements are CD30+¹². For prognostic purposes, it is important to note that immunohistochemical markers (e.g. CD10, Bcl6 and MUM1) can indicate the type of cell of origin in DLBCL and some (e.g. Bcl2 and c-Myc) can have a role in differentiating NOS forms from high grade lymphomas¹³.

The evidence of lymphoma on kidney biopsy leads to an important differential diagnosis between the rare kidney-limited form and systemic lymphoproliferative

disorder involving the kidney. The absence of extrarenal localization with appropriate clinical staging could be indicative of primary kidney lymphoma, which accounts for about 0.7% of all extranodal lymphomas in North America¹⁴, the most frequent subtype being DLBCL¹⁵. These forms show a poor outcome with a reported 1-year mortality rate as high as 75%¹⁶ and a 5-year survival rate of only 40-50% with median survival time of 8 months to 3 years¹⁷. On the other hand, the detection of extrarenal sites involved by lymphoma may be revealed by comprehensive staging, and thus lead to a diagnosis of systemic lymphoproliferative disorder presenting with kidney involvement, with important consequences for the prognosis and therapy, as demonstrated in this case. Because of the important prognostic ramifications, this case report illustrates the vital importance of careful evaluation of the kidney biopsy and appropriate recognition of the differential diagnosis in order to guide the subsequent hematologic evaluation.

Article Information

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Box 1.

Key pathology findings in kidney lymphoma.

1. Extensive or complete obliteration of the parenchyma
2. Dense infiltrate mainly composed of a mixture of small lymphoid appearing cells, some spindly cells and cells with enlarged atypical nuclei
3. Diffuse positivity of the neoplastic elements for B-cell lineage antigens in immunohistochemistry (eg. CD20, CD79a and PAX5)
4. High proliferative rate assessed through ki-67 immunohistochemistry (usually >40% in DLBCL cases)
5. Variable expression of additional immunohistochemical markers to define the cell of origin (CD10, Bcl6, MUM1) or to identify high-grade lymphomas (c-Myc and Bcl2)

Figure Legend

Figure 1. An extensive infiltrate obliterated the kidney parenchyma (A, hematoxylin and eosin, magnification x50), composed of a mixture of small lymphoid appearing cells, some spindly cells and cells with enlarged atypical nuclei (B, hematoxylin and eosin, magnification x200 and inset magnification x400). Atypical cells were diffusely positive for CD20 (C) and Bcl6 (D, top of the picture) with 70-80% Ki-67 positivity (D, bottom of the picture) (magnification x10, insets magnification x40).

References

1. Richmond J, Sherman RS, Diamond HD, Craver LF. Renal lesions associated with malignant lymphomas. *Am J Med.* 1962;32(2):184-207.
2. Obrador GT, Price B, O'Meara Y, Salant DJ. Acute renal failure due to lymphomatous infiltration of the kidneys. *J Am Soc Nephrol.* 1997;8(8):1348-1354.
3. Villa D, Connors JM, Sehn LH, Gascoyne RD, Savage KJ. Diffuse large B-cell lymphoma with involvement of the kidney: outcome and risk of central nervous system relapse. *Haematologica.* 2011;96(7):1002-1007.
4. Törnroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. *Am J Kidney Dis.* 2003;42(5):960-971.
5. Chen X, Hu D, Fang L, et al. Primary renal lymphoma: A case report and literature review. *Oncol Lett.* 2016;12(5):4001-4008.
6. 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.
7. Cohen LJ, Rennke HG, Laubach JP, Humphreys BD. The spectrum of kidney involvement in lymphoma: a case report and review of the literature. *Am J Kidney Dis.* 2010;56(6):1191-1196.
8. Sunnawar A, Menias CO, Ojili V, et al. Abdominal manifestations of histiocytic disorders in adults: imaging perspective. *Br J Radiol.* 2016;89(1065):20160221.
9. Luciano RL, Brewster UC. Kidney involvement in leukemia and lymphoma. *Adv Chronic Kidney Dis.* 2014;21(1):27-35.
10. Okamoto A, Yanada M, Inaguma Y, et al. The prognostic significance of EBV DNA load and EBER status in diagnostic specimens from diffuse large B-cell lymphoma patients. *Hematol Oncol.* 2017;35(1):87-93.
11. Lopez A, Abrisqueta P. Plasmablastic lymphoma: current perspectives. *Blood Lymphat Cancer.* 2018;8:63-70.
12. Tsuyama N, Sakamoto K, Sakata S, Dobashi A, Takeuchi K. Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. *J Clin Exp Hematop.* 2017;57(3):120-142.
13. Campo E, Harris NL, Pileri SA, Jaffe ES, Stein H, Thiele J. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* IARC Who Classification of Tumours; 2017.

14. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer*. 1972;29(1):252-260.
15. Lontos K, Tsagianni A, Msaouel P, Appleman LJ, Nasioudis D. Primary urinary tract lymphoma: rare but aggressive. *Anticancer Res*. 2017;37(12):6989-6995.
16. Porcaro AB, D'Amico A, Novella G, et al. Primary lymphoma of the kidney. Report of a case and update of the literature. *Arch Ital Urol Androl*. 2002;74(1):44-47.
17. Ladha A, Haider G. Primary renal lymphoma. *J Coll Physicians Surg Pak*. 2008;18(9):584-585.

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