J Interdiscipl Histopathol 2013; 1(2): 93-97 *ISSN: 2146-8362*

Case Report

Double-Hit Lymphoma Presenting as Primary Renal Lymphoma: A Case Report

Vikas Mehta[1], Chandy Ellimottil[2], Jodi Speiser[1], Milind Velankar[1], Güliz A Barkan[1]

Loyola University Chicago, Stritch School of Medicine, Department of Pathology[1] and Urology[2], Chicago, IL, USA

Received: January 14, 2013

Accepted: January 21, 2013

Published Online: January 28, 2013

DOI: 10.5455/jihp.20130121075815

Corresponding Author:
Güliz A Barkan,
Loyola University Medical Center
gbarkan@lumc.edu

Keywords: Primary renal lymphoma, double hit lymphoma

Abstract

B-cell lymphomas with concurrent MYC with BCL2 and/or BCL6 rearrangements, also known as "double hit" lymphomas (DHL), are rare neoplasms characterized by highly aggressive clinical behavior, complex karyotypes, and a spectrum of pathological features overlapping with Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Primary renal lymphoma (PRL) by definition is a renal lymphoma without evidence of systemic involvement. PRL is extremely rare with less than 100 cases of both Hodgkin disease and non-Hodgkin lymphoma reported in literature. Double hit lymphomas have extremely poor prognosis, and high resistance to intensive chemotherapy, including high-dose chemotherapy. We describe a very rare case of DHL arising in kidney as PRL in whom concurrent MYC and IGH-BCL2 rearrangements were detected.

INTRODUCTION

B-cell lymphomas with concurrent MYC with BCL2 and/or BCL6 rearrangements, also known as "double hit" lymphomas (DHL), are rare neoplasms characterized by highly aggressive clinical behavior, complex karyotypes, and a spectrum of pathological features overlapping with Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). It is considered that BCL2 translocation precedes MYC events in lymphomagenesis of DHL. Double hit lymphomas have extremely poor prognosis, and high resistance to intensive chemotherapy, including high-dose chemotherapy. We describe a very rare case of DHL arising in kidney as Primary renal lymphoma (PRL) in whom concurrent *MYC* and *IGH-BCL2* rearrangements were detected.

CASE REPORT

An 82-year-old female, with past medical history significant for coronary artery disease, and recurrent deep vein thrombosis (DVC) presented to the emergency room after a fall. Her physical examination and laboratory work-up, including white blood cell count and liver function tests, were unremarkable except for an elevated BUN, creatinine and serum calcium (36 mg/dl (normal 7-22 mg/dl), 2.34 mg/dl (normal 0.6-1.4 mg/dl),15.7 mg/dl (normal 8.5 - 10.5 mg/dl), respectively). Renal ultrasound revealed a 14 cm heterogeneous right renal mass. Subsequent computed tomography (CT) of her chest, abdomen and pelvis without contrast, revealed several bilateral pulmonary nodules that were too small to characterize. The renal mass was shown to be causing a mass effect on the IVC, liver, and duodenum with no definite extension into the right renal vein or IVC (Figure 1A and B). She was placed on cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP). After cycle #3 of R-CHOP, repeat CT chest/abdomen/pelvis showed dramatic volume reduction of the renal mass.

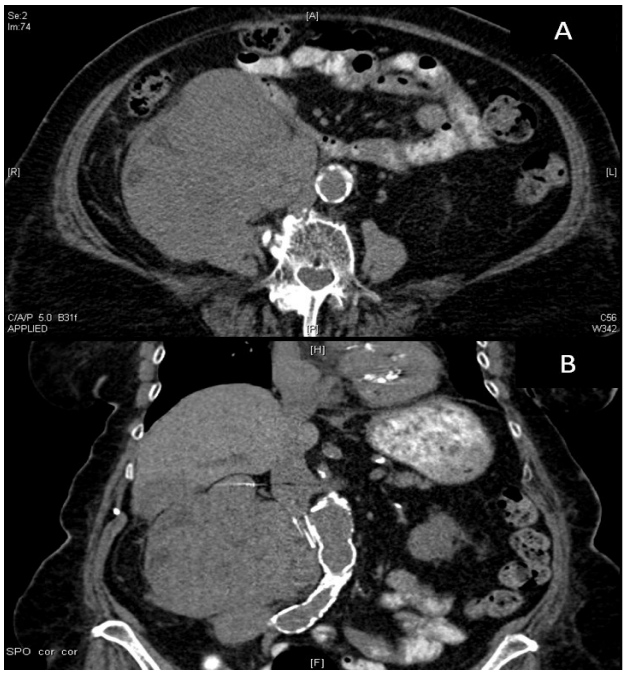

Figure 1. A. Large renal mass. **B.** Mass effect on liver, IVC, duodenum

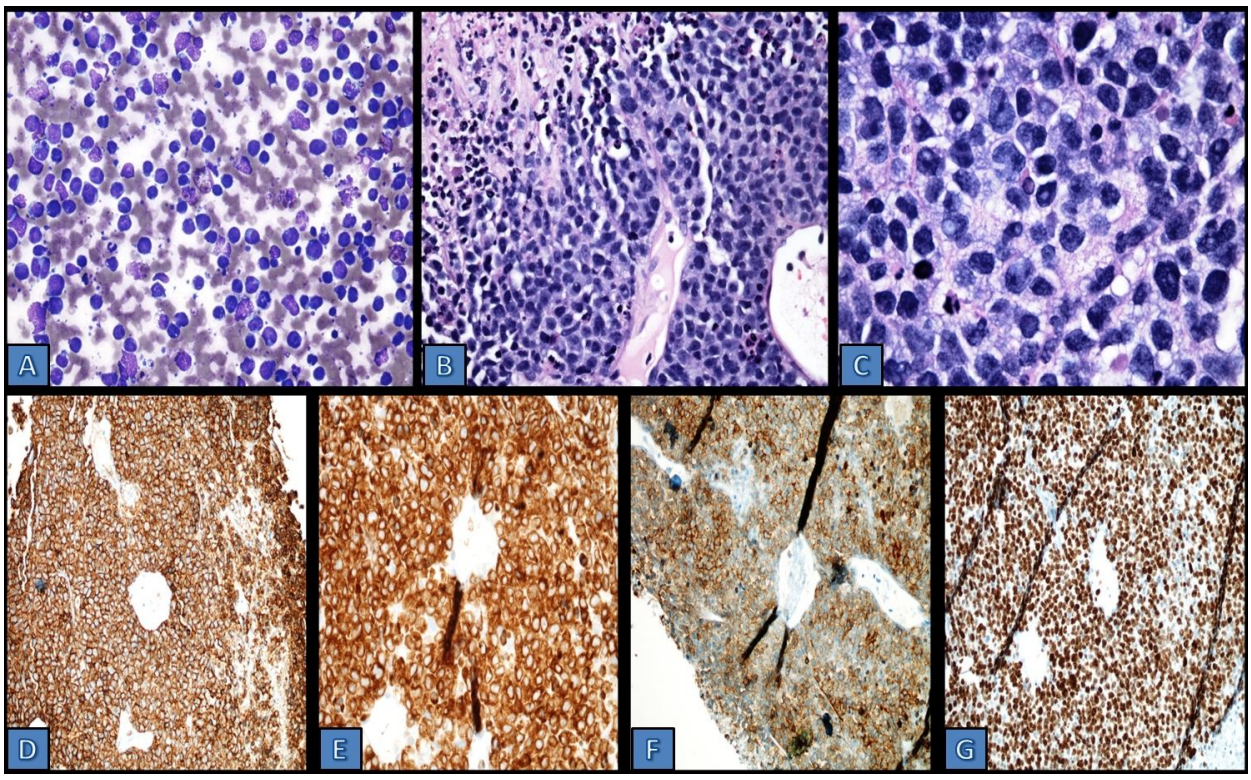

Figure 2. A. Fine needle aspiration of the renal mass revealed a cellular smear comprising of large lymphoid cells with irregular high-grade cytologic features, including prominent nucleoli and finely dispersed and immature-appearing chromatin. **B**. Core biopsy of the renal mass showed diffuse infiltration by neoplastic lymphoid infiltrate with focal areas of necrosis (H&E, x200). **C**. The tumor cells were medium-to large-size with prominent nucleoli (H&E, x400). **D-F**. The tumor cells were positive for CD20 [D], BCL-2 [E], CD10 [F]. **G.** Ki67 stain showed proliferation fraction of 95% (IHC, x100 for E-G).

Pathologic findings

Fine needle aspiration of the renal mass revealed a cellular smear comprising of single or small clusters of large lymphoid cells with scant cytoplasm, high nuclear cytoplasmic ratio, prominent nucleoli and finely dispersed and immature-appearing chromatin (Figure 2A). Core biopsy of the renal mass showed diffuse infiltration by neoplastic lymphoid infiltrate (Figure 2B), composed of medium-to large-size lymphoid cells with focal areas of necrosis (Figure 2C). The tumor cells were positive for CD20 (Figure 2D), BCL-2 (Figure 2E), CD10 (Figure 2F), CD5 (weakly in some neoplastic cells) and negative for CD3, MUM1, TdT, and BCL-1. Ki67 stain showed proliferation fraction of 95% (Figure 2G). Fluorescent in situ hybridization (FISH) studies detected *IgH/BCL2* fusion in 91.5% of the interphase cells and specifically, these results were positive for a t(14;18)(q32;q21). Additional studies (breakapart probe for *MYC* by FISH) also detected a rearrangement of the *c-MYC* gene region at 8q24 in 95% of the cells analyzed; however, studies were negative for a t(8;14)(q24;q32), indicating that although there was no evidence of t(8;14), a translocation involving *MYC* (partner unknown) was also detected. The FISH study for t(11;14) was negative. In the light of these data, based on the WHO Classification (4th Edition) criteria, the diagnosis of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (double hit lymphoma) was made. Subsequently a bone marrow biopsy was done which showed no involvement by the lymphoma.

DISCUSSION

Kidney is the second most common site for metastasis in patients with non-Hodgkin's lymphoma [1]. However, primary renal lymphoma is extremely rare [2, 3]. PRL is defined as: (a) the presence of a renal mass without extrarenal lymphomatous involvement, (b) the absence of a leukemic blood picture, and (c) the absence of lymphadenopathy or hepatosplenomegaly [4, 5]. PRL seems to show a sex predisposition for males and typical age of presentation is typically above 40; however, cases have been reported in individuals as young as 21 [5, 6]. Clinical presentation of the disease can be characterized by flank pain, weakness, weight loss, hematuria, malaise, abdominal mass, thrombocytopenia, and/or renal failure [7]. The etiology of PRL is still unknown, as the kidney does not have lymphoid tissue. Repeated injury to renal lymphatics as a result of chronic inflammation has been suggested as the cause of lymphoid transformation and subsequent neoplasia of the lymphoid tissue; a process similar to that of other extranodal mucosa-associated lymphoid tissue (MALT) lymphomas, affecting skin, breast, and other non-lymphoid tissues[1, 8]. Diagnosis is challenging, and may often occur after nephrectomy since these tumors mimic renal cell carcinoma. It is essential, however, to distinguish between the two, as management is completely different. A pre-operative FNA and/or core biopsy is essential to confirm the diagnosis in suspected patients. PET scan has also been demonstrated to be a potential method of detection of extranodal lymphoma; however, its efficacy is still under investigation [9].

DHL is now described as a well-characterized group in the category of B-cell lymphoma with a spectrum of pathological features overlapping with Burkitt lymphoma and diffuse large B-cell lymphoma in the WHO classification 2008 [10]. Double-hit lymphomas comprise about 3-5% of high grade B cell lymphomas and are characterized by concurrent MYC with BCL2 and/or BCL6 rearrangements, highly aggressive clinical behavior and complex karyotypes and have a high progression ability. The DHL progresses to extranodal lesions such as in the bone marrow, central nervous system, and gastrointestinal tract [11-15]. A complex karyotype including both *BCL2* and *MYC* translocations is recognized [11, 14]. Morphologically, DHL is composed of cells that show greater variability in cellular morphology among different cases. Starry sky macrophages are typically present, as well as many mitotic figures and prominent apoptotic figures, causing a resemblance to Burkitt lymphoma (BL). In some cases the cells resemble BL, but with more variation in size and shape than considered acceptable for BL. While still some other cases can have large nuclear size or nuclear size intermediate between BL and DLBCL. Lymphoma cells are generally positive for CD19, CD20, CD22, CD79a, and negative for surface light chains; BCL-2 can be positive in many cases; BCl-2 positivity in an otherwise typical Burkitt lymphoma should raise suspicion for a DHL. CD10 and BCl-6 are generally positive (indicating germinal center origin), however, cases negative for BCl-2, CD10 and BCl-6 immunostains have also been described [3, 5, 8, 10]. The proliferation (Ki-67) rate in most studies is variable and ranges from 60 to 100% [12].

DHL has a high resistance to intensive chemotherapy, including high-dose chemotherapy followed by stem cell transplantation [3, 14]. Patient prognosis is poor, and over half of all DHL patients die within 1 year [3, 5, 7, 8, 10, 14]. The high chemoresistance in DHL is considered to be due to the synergistic actions of apoptotic inhibition due to deregulation of BCL2 and the enhanced proliferation due to deregulation of *MYC* [16]. Parker et al. reported two cases of DHL successfully treated with an aggressive immunochemotherapy regimen, autologous stem cell

transplantation, and radiation therapy: No recurrence of the disease was seen in the radiation field in the first patient, and no recurrence in the second patient was observed after total body irradiation (TBl), suggesting that radiation therapy may be beneficial for patients with DHL, and that up-front TBI based hematopoietic stem cell transplantation could potentially produce sustained complete remission for DHL [17]. Early recognition of DHL is important for considering upfront TBI-based hematopoietic stem cell transplantation. However, it is important to note that DHL cannot be diagnosed without chromosomal analysis. Close examination, including chromosomal analysis including, if needed, paraffin section FISH studies, is therefore desirable for all patients with high-grade B-cell lymphoma and in cases of suspected recurrence of this lymphoma.

DHL presenting as PRL is an extremely rare diagnosis in patients presenting with a renal mass. The clinical, morphologic, and immunophenotypic findings suggest that most lymphoid neoplasms with dual translocations of t(14;18) and *MYC* gene rearrangement are high grade with clinical and morphologic features in-between Burkitt and diffuse large B-cell lymphoma. Dissemination to extrarenal sites is common and confers a bad prognosis as well [18]. In PRL, proper treatment and early intervention have been documented to correlate with improved outcomes [19, 20]. A comprehensive cytogenetic analysis of *BCL2* and *MYC* status on all aggressive lymphomas may identify a group of high-risk patients who may benefit from chemotherapeutic regimens that include rituximab and/or BCL2-targeted therapy [18]. As affected patients have poor prognosis despite aggressive therapy, knowledge of the presence of both translocations has prognostic value and thus conventional cytogenetic analysis is warranted. For cases without conventional cytogenetic data, FISH analysis is useful in confirming the presence of *c-MYC* rearrangement in high-grade B-cell lymphoma displaying Burkitt or atypical Burkitt morphology.

REFERENCES

1. Salem Y, Pagliaro LC, Manyak MJ. Primary small noncleaved cell lymphoma of kidney. Urology 1993; 42(3): 331-335.
2. Kandel LB, McCullough DL, Harrison LH, Woodruff RD, Ahl ET Jr, Munitz HA. Primary renal lymphoma. Does it exist? Cancer 1987; 60(3): 386-391.
3. Okuno SH, Hoyer JD, Ristow K, Witzig TE. Primary renal non-Hodgkin's lymphoma. An unusual extranodal site. Cancer 1995; 75(9): 2258-2261.
4. Qiu L, Unger PD, Dillon RW, Strauchen JA. Low-grade mucosa-associated lymphoid tissue lymphoma involving the kidney: report of 3 cases and review of the literature. Archives of Pathology & Laboratory Medicine 2006; 130(1): 86-89.
5. Tuzel E, Mungan MU, Yorukoglu K, Basakci A, Kirkali Z. Primary renal lymphoma of mucosa-associated lymphoid tissue. Urology 2003; 61(2): 463.
6. Olusanya AA, Huff G, Adeleye O, Faulkner M, Burnette R, Thompson H, Adeola T, Woods K. Primary renal non-Hodgkins lymphoma presenting with acute renal failure. Journal of the National Medical Association 2003; 95(3): 220-224.
7. Kose F, Sakalli H, Mertsoylu H, Sezer A, Kocer E, Tokmak N, Kilinc F, Ozyilkan O. Primary renal lymphoma: report of four cases. Onkologie 2009; 32(4): 200-202.
8. Freeman, C, Berg JW, Cutler, SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972; 29(1): 252-260.
9. Al-Salam S, Shaaban A, Alketbi M, Haq NU, Abouchacra S. Acute kidney injury secondary to renal large B-cell lymphoma: role of early renal biopsy. International Urology and Nephrology 2011; 43(1): 237-240.
10. Kluin PM, Harris NL, Stein H, Leoncini L, Raphael M, Campo E, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. In: Swerdlow SH, Campo E, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed, Lyon, IARC Press, pp. 265-266, 2008.
11. Kanungo A, Medeiros LJ, Abruzzo LV, Lin P. Lymphoid neoplasms associated with concurrent t(14;18) and 8q24/c-MYC translocation generally have a poor prognosis. Modern Pathology 2006; 19(1): 25-33.
12. Lin P, Medeiros LJ. High-grade B-cell lymphoma/leukemia associated with t(14;18) and 8q24/MYC rearrangement: a neoplasm of germinal center immunophenotype with poor prognosis. Haematologica 2007; 92(10): 1297-1301.
13. Johnson NA, Savage KJ, Ludkovski O, Ben-Neriah S, Woods R, Steidl C, Dyer MJ, Siebert R, Kuruvilla J, Klasa R, Connors JM, Gascoyne RD, Horsman DE. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009; 114(11): 2273-2279.
14. Tomita N, Tokunaka M, Nakamura N, Takeuchi K, Koike J, Motomura S, Miyamoto K, Kikuchi A, Hyo R, Yakushijin Y, Masaki Y, Fujii S, Hayashi T, Ishigatsubo Y, Miura I. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica 2009; 94(7): 935-943.
15. Niitsu N, Okamoto M, Miura I, Hirano M. Clinical features and prognosis of de novo diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations.

Leukemia 2009; 23(4): 777-783.

16. Aukema SM, Siebert R, Schuuring E, van Imhoff GW, Kluin-Nelemans HC, Boerma EJ, Kluin PM. Double-hit B-cell lymphomas. Blood 2011; 117(8): 2319-2331.
17. Parker SM, Olteanu H, Vantuinen P, Lawton CA, Schultz CJ, Christians KK, Fenske TS. Follicular lymphoma transformation to dual translocated Burkitt-like lymphoma: improved disease control associated with radiation therapy. International Journal of Hematology 2009; 90(5): 616-622.
18. Dimopoulos MA, Moulopoulos LA, Costantinides C, Deliveliotis C, Pantazopoulos D, Dimopoulos C. Primary renal lymphoma: a clinical and radiological study. The Journal of Urology 1996; 155(6): 1865-1867.
19. Porcaro AB, D'Amico A, Novella G, Curti P, Ficarra V, Antoniolli SZ, Martignoni G, Matteo B, Malossini G. Primary lymphoma of the kidney. Report of a case and update of the literature. Arch Ital Urol Androl 2002; 74(1): 44-47.
20. Van Gelder T, Michiels JJ, Mulder AH, Klooswijk AI, Schalekamp MA. Renal insufficiency due to bilateral primary renal lymphoma. Nephron 1992; 60(1): 108-110.