RESEARCH COMMUNICATION

Renal Involvement in Non-Hodgkin's Lymphoma: The Shaukat Khanum Experience

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Abstract

Background: Primary lymphoma of genitourinary system is rare as these organs do not contain lymphoid tissue, however secondary involvement often occurs. The most commonly affected genitourinary organ is the kidney. Methods: Medical records of 901 patients with documented NHL seen at Shaukat Khanum Memorial Cancer Hospital & Research Center during 1995-2003 were studied for the incidence, histopathological, clinical and radiological correlation of renal involvement in NHL. Results: 19(2.1%) patients had renal involvement. Male to female ratio was 3.75:1. Histology was diffuse large cell lymphoma in 12(63%) patients. IPI was High, High intermediate and Low intermediate in 17(89.5%) patients. Radiologically, 5(26.5%) patients had the disease above the diaphragm, 2(10.5%) patients had disease below the diaphragm while 12(63%) had disease on both sides of the diaphragm. 11(58%) showed complete response, 1(5.5%) showed partial response while 7(36.8%) showed progressive disease. Conclusion: Majority of patients with renal involvement had low intermediate or higher IPI compatible with significant progression rate. The findings and disease behavior in our population is comparable to those quoted in English literature. Radiological tools have made it easier to monitor disease response and renal biopsy is seldom required.

Key Words: Non-Hodgkin's lymphoma - primary renal lymphoma - renal failure

Introduction

Renal involvement is a relatively uncommon clinical presentation (Yasunaga et al.,1997) of Non-Hodgkin's lymphoma. When it does occur, it is usually due to secondary involvement rather than primary lymphoma. As kidneys do not have lymphoid tissue, the origin of primary renal lymphoma (PRL) is controversial. The frequency of primary renal lymphoma in North America is reported at 0.7% of all extranodal lymphomas (Freeman et al.,1972) while a study in Japan indicated it to be 0.1% (Aozasa et al.,1985). On the other hand, secondary renal involvement is quite common in comparison to PRL and occurs in disseminated disease. Autopsy findings show over 50% advanced cases may have renal involvement (Kandell et al., 1987; Xiano et al.,1997). Due to the small number of studies (Kandell et al.,1987; Okuno, 1995) performed on PRL, information is very limited. Acute renal failure is a common manifestation of primary renal NHL with a poor prognosis (Kandell et al.,1987; Harris and Lager, 1991; Arija et al.,1994; Okuno, 1995), but long-term survivors have been occasionally reported after surgical resection or combination chemotherapy (Ferry et al., 1993; Arija et al.,1994; Malbrain et al.,1994; Choi et al.,1997).

We here reviewed medical records of cases with non-Hodgkin's lymphomas enrolled in our hospital between 1995-2003 to look at the incidence, sex distribution, pattern, histological diagnosis and response to therapy of patient with renal involvement.

Patients and Methods

There were a total of 961 documented cases of adult NHL at Shaukat Khanum Memorial Cancer Hospital & Research Centre. Only those cases were included who underwent complete initial staging work-up including a thorough clinical examination, complete hematological, histopathological examination, renal and hepatic functional evaluation, bone marrow examination, radiological imaging including appropriate CT scan and/ or MRI. Ultrasonography was utilized as per clinical picture in addition to CT scan results. This led to exclusion of 60 patients from the analysis.

The criteria for renal involvement were (i) varying degree of renal failure, (ii) enlargement of kidney without obstruction (iii) absence of other causes of renal failure & (iv) absence of other renal abnormalities.

Impaired renal function was defined as having decreased urinary output, presence of proteinuria, increased levels of BUN(normal range 7-21 mg/dl) and serum creatinine (normal range 0.8-1.5 mg/dl).

Pre-renal and post-renal causes of renal failure were excluded using data from the initial workup.

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Tumor lysis syndrome (Hande and Garrow,1993; Jasel and Day,1994) was excluded and defined as having at least 2 of the following:
1. Increased serum potassium(normal 3.6-5.0 mg/dl)
2. Increased serum uric acid(normal 3.4-7.0 mg/dl)
3. Increased serum phosphate(normal 2.5-4.5 mg/dl)
4. Decreased serum calcium(8.4-10.2 mg/dl)

The reference ranges for all lab values are the standard used by the Department of Pathology, Shaukat Khanum Hospital at that time.

The International prognostic index was used to predict risk of disease recurrence and overall survival. Depending on the number of factors present, disease is stratified into High (4 or 5 factors), High Intermediate (3 factors), Low Intermediate (2 factors) and Low (0 or 1 factors) risk groups. Patients with two or more risk factors have less than a 50% chance of relapse-free and overall survival at 5 years (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 2003).

The updated REAL/WHO classification was used in cellular stratification of the disease. The WHO modification of the REAL classification recognizes 3 major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasm, T-cell/

Table 1. Data for the Series of Lymphomas

Age/Sex	Histology	Renal Involvement	Renal Failure	Nodal Areas	Extranodal Sites	Renal Biopsy	CT Scan	Disease Response
41/F	Diffuse Large Cell Lymphoma (DLCL)	Bilateral	No	Waldeyer's Ring & Neck	CNS	No	Yes	Complete Response (CR)
43/F	DLCL	Bilateral	No	Neck, Mediastinum, Abd. & Pelvis	Spleen, Liver	No	Yes	CR
62/F	DLCL	Bilateral	No	Neck, Abd. & Pelvis	Liver	No	Yes	Progressive
68/F	DLCL	Right-sided	No	Neck,Axilla,Abd & Inguinal	None	No	Yes	CR
25/M	DLCL	Right-sided	No	Abd & Pelvis	Bowel	No	Yes	Progressive
26/M	DLCL	Bilateral	No	Mediastinum, Abd.& Pelvis	None	No	Yes	CR
30/M	DLCL	Bilateral	No	Neck, Mediastinum & Axilla	CNS	No	Yes	CR
38/M	DLCL	Left-sided	No	Abd. & Pelvis	Stomach	No	Yes	CR
43/M	DLCL	Bilateral	Yes	Axilla,Abd. & Inguinal	None	No	Yes	Progressice
50/M	DLCL	Right-sided	No	Neck, Mediastinum, Pelvis& Inguinal	None	No	Yes	CR
52/M	DLCL	Left-sided	No	Neck, Mediastinum	None	Yes	Yes	Progressive
63/M	DLCL	Bilateral	No	Neck, Mediastinum, Axilla, Pelvis	None	No	Yes	CR
20/M	T-lymphoblastic lymphoma	Bilateral	No	Neck, Mediastinum, Axilla	Bone marrow	No	Yes	Progressive
22/M	T-lymphoblastic lymphoma	Bilateral	No	Neck, Mediastinum, Axilla,Abd & Inguinal	Liver, Bone marrow	No	Yes	CR
24/M	T-lymphoblastic lymphoma	Bilateral	Yes	Neck, Mediastinum, Axilla	Liver	No	Yes	CR
65/M	Diffuse follicular small cell lymphoma	Left-sided	No	Mediastinum, Axilla,Inguinal	Sinuses	No	Yes	CR
46/M	Diffuse follicular small cell lymphoma	Bilateral	No	Neck,Axilla, Inguinal	Spleen, Bone marrow	No	Yes	Progressive
55/M	Diffuse Follicular lymphoma	Bilateral	No	Axilla,Abd Pelvis & Inguinal	Spleen, Bone marrow	No	Yes	Partial response
37/M	Burkitt's lymphoma	Left-sided	No	Axilla, Abd. & Inguinal	Spleen, Liver, Bone marrow	No	Yes	Progressive

natural killer (NK)-cell neoplasm, and Hodgkin's lymphoma. Both lymphomas and lymphoid leukemias are included in this classification because both solid and circulating phases are present in many lymphoid neoplasms and distinction between them is artificial.

Results

In accordance with the set criteria, we found 19 (2.1%) patients who had renal involvement. 12(63%) patients presented with bilateral localization and 7(37%) showed unilateral disease. The clinical and pathological features are listed in Table 1. The male to female ratio was 3.75 to 1.16/19 (84.2%) patients had aggressive lymphomas while 3/19 (15.8%) had indolent lymphomas. Histology was diffuse large cell lymphoma in 12(63%) patients, T-lymphoblastic lymphoma in 3(15.8%) patients, diffuse follicular small cell lymphoma (Grade I) in 2(10.5%) patients and 1 (5.3%) each with follicular mixed cell (Grade II) & Burkitt's lymphoma. IPI was High in 4(21%) patients, High intermediate in 6(31.5%) patients, Low intermediate in 7(37%) patients and Low in 2(10.5%) patients.

Radiologically, 5(26.5%) patients had disease above the diaphragm only, 2(10.5%) patients had disease below the diaphragm only, while 12(63%) had disease on both sides. 13(68.5%) patients had other extranodal sites in addition to the kidneys. 2(10.5%) patients with bilateral renal involvement also had CNS involvement. 1(5.2%) presented with renal mass where the diagnosis was established after nephrectomy. Of the 19 patients, 15(79%) patients received 6 or more cycles of the selected regimen. The chosen chemotherapy was CHOP in 11 (58%) patients, HyperCVAD in 3(15.8%); ESHAP in 2(10.5%) while 3(15.8%) patients expired before chemotherapy could be administered. 11(58%) showed complete response, 1(5.5%) showed partial response while 7(36.8%) showed progressive disease. The response in terms of renal disease was determined by renal function tests and CT scan reports.

Discussion

Kidneys are mostly secondarily involved by lymphoproliferative disorders. The pathogenesis of primary renal lymphoma (PRL) is poorly understood. One view is that a chronic infection in the kidney recruits lymphoid cells into the renal parenchyma, during which an oncogenic event takes place (Duannay, 1940). Another explanation is that lymphomas arise in the renal capsule, which is rich in lymphatics, and invade the renal parenchyma secondarily (Salem et al., 1993). Another possible origin of primary renal lymphoma is a lymphomatous process in the perirenal adipose tissue with secondary involvement of the kidney (Betta et al.,1986). The criteria (Kandell et al.,1987; Malbrain et al.,1994) generally accepted for PRL should have:

1. Renal failure as initial presentation
2. Enlargement of kidneys without obstruction and other organ or nodal involvement.
3. Absence of other causes of renal failure
4. Diagnosis made by renal biopsy
5. Rapid improvement of renal function after therapy

While searching in the Medline for PRL, a total of 83 cases were found. This included both adult and pediatric patients. Although the primary authors on the initial reports have reported these as primary renal lymphomas, more recent stringent criteria described as above by some reviews argue against the initial assessments of many of these cases. Strictly adhering to the above criteria for PRL would decrease the number cases to half. This is attributed to two reasons; firstly, there has been a decrease in number of renal biopsies being performed because of reliance on diagnostic application of radiological tools and secondly, advanced disease presentation usually involving some nodal or extranodal areas apart from the kidney, as was the case at our institution where the patients presented with advanced disease making it very difficult to assess the origin of the lymphoma as renal. In the literature reviewed, most pediatric cases had bilateral kidney disease while there are more unilateral presentations in adult cases with male preponderance (Camitta et al.,1986; Kutluk et al.,1989; Dobkin et al.,1991; Arija et al.,1994). We found majority of our cases in the adults to be bilateral with more involvement in the males. The IPI in all the patients has at least one factor or more which is consistent with our findings. Renal failure is the most common complication of PRL (Kandell et al.,1987; Harris and Lager,1991; Arija et al.,1994; Malbrain et al.,1994) and was the initial presentation in only 39 of the 83 cases.

In this review, we have found 2 cases that can be considered as PRL if renal biopsy is excluded from criteria used by western studies and 12 cases can be put under the same umbrella if renal failure is not used as a mandatory presentation. A significant number of our patients with renal involvement were in the low intermediate to high risk group according to the IPI index and therefore, relapsed or progressed after treatment. In our opinion, subjecting a patient to a renal biopsy without renal dysfunction is not necessary when evidence of lymphoma in other sites is available. We did not come across any changed therapeutic recommendations for lymphoma with renal involvement although one has to be more vigilant in following the renal function and tumor lysis syndrome in these patients.

References

The International Non-Hodgkin's Lymphoma Prognostic Factors Project (2003). A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med, 329, 987-94.

Aozasa K, Tsujimoto M, Sukarai M, et al (1985). Non-Hodgkin's lymphoma in Osaka, Japan. *Eur J Cancer Clin Oncol*, **21**, 487-92.

Arija J M, Carrion JR, Garcia FR, et al (1994). Primary renal lymphoma: Report of 3 cases and review of the literature. *Am J Nephrol*, **14**, 148-53.

Betta PG, Bottero G, Cosimi MF,et al (1986). Primary renal lymphoma. *Eur Urol*, **12**, 352-4.

Camitta BM, Casper JT, Kun LE (1986). Isolated bilateral T-cell renal lymphoblastic lymphoma. *Am J Pediatr Hematol Oncol*, **8**, 8-12.

Choi JH, Choi GB, Shim KN, et al (1997). Bilateral primary renal non-Hodgkin's lymphoma presenting with acute renal failure: successful treatment with systemic chemotherapy. *Acta Haematol*, **97**, 231-5.

Dobkin SF, Brem AS, Caldamone AA (1991). Primary renal lymphoma. *J Urol*,**146**, 1588-90.

Duanay PN (1940). Linfosarcoma y linfosarcomatosis des los rinones: part II. *Rev Med Trop Parasitol Bacteriol Clin Lab*, **6**, 213.

Ferry JA, Harris NL, Papanicolaou N, et al (1993). Lymphoma of the kidney: A report of 11 cases. *Am J Surg Pathol* , **19**, 134-44.

Freeman C, Berg JW, Culter SJ (1972).Occurrence and Prognosis of extranodal lymphomas. Cancer, **29**,252-60.

Hande KR, Garrow GC (1993). Acute tumor lysis syndrome in patients with high grade non-Hodgkin's lymphoma. *Am J Med* , **94**,133-39.

Harris GJ, Lager DJ (1991). Primary renal lymphoma. *J Surg Oncol*, **46**, 273-7.

Jasel AM, Day JH (1994). Acute tumor lysis syndrome. *Am J Hematol*, **47**, 129-31.

Kandell LB, McCullough DL, Harrison LH,et al (1987). Primary renal lymphoma. Does it really exist?Cancer, **60**, 386-91.

Kutluk MT, Büyükpamukçu M, Gögüs S (1989). Renal lymphoma. An unusual presentation in a child. *Turk J Pediatr*, **31**, 71-7.

Malbrain MLNG, Lambrecht GLY, Daelemans R, et al(1994). Acute renal failure due to bilateral lymphomatous infiltrates. Primary extranodal non-Hodgkin's lymphoma (p-EN-NHL) of the kidneys: Does it really exist? *Clin Nephrol*, **42**, 163-9.

Okuno SH, Hoyer JD, Ristow K, et al (1995). Primary renal non Hodgkin's Iymphoma. An unusual extranodal site. *Cancer,* **75,** 2258-61.

Salem Y, Pagliaro LC, Manyak MJ (1993). Primary small noncleaved cell lymphoma of kidney. Urology , **42**, 331-5.

Xiano JC, Mattmuller W, Ruck P,et al (1997). Renal involvement in myeloproliferative and lymphoproliferative disorders, a study of autopsy cases. *Gen Diagn Pathol*, **142**, 147-53.

Yasunaga Y, Hoshido Y, Hashimoto M, et al(1997) Malignant lymphoma of kidney. *J Surg Oncol***, 64,** 207-11.