

Primary Diffuse large B-Cell lymphoma of testis: A single centre experience and review of literature

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Abstract

Background: Primary testicular lymphoma constitutes 1-2% of Non-Hodgkin's lymphomas affecting elderly men >60 years of age. Most often it is a Diffuse large B cell lymphoma (DLBCL) and treatment involves multimodality approach involving surgery, chemotherapy and radiotherapy. Outcome remains poor in spite of aggressive therapy.

Materials and Methods: We retrospectively reviewed 286 registered cases of DLBCL (aged >14 years) from 2007 to 2011 and found nine primary testicular involvement patients. These cases were analyzed for baseline clinical features, investigations, staging, treatment and outcome.

Results: Median age was 58 (46-76) years. All patients presented with testicular swelling, two had the presence of B symptoms, and three with abdominal lymphadenopathy. Six had stage IE disease and three patients had stage IIE. All patients underwent orchiectomy. Eight patients received combination chemotherapy and six completed three or more cycles. Four achieved complete response, among these three relapsed after 32, 42, 70 months and one was lost to follow up. Two had a progressive disease, among these one died of disease and one alive with disease. Complete follow up was available from five patients and median survival was 36 months (11-78 months).

Conclusion: Primary testicular DLBCL is uncommon, needs multimodality treatment and central nervous system prophylaxis to improve the survival. The outcome needs to be further investigated using biological approaches (Rituximab based) and/or more aggressive management.

Key Words: Diffuse large B cell lymphoma, Non-Hodgkin's lymphoma, testis

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INTRODUCTION

Primary testicular lymphoma (PTL) constitutes 1-2% of Non-Hodgkin's lymphoma (NHL), 4% of extranodal NHL and varying 1-10% of testicular neoplasms affecting

elderly men greater than 60 years of age, with a grave prognosis.^[1,2] The most frequent histology is Diffuse large B-cell lymphoma (DLBCL) and has a predilection for extra nodal sites, especially the contra lateral testis and central nervous system (CNS).^[3,4] The incidence has increased over the last two decades with the emergence of human immune deficiency virus infection.^[5] There is no consensus till date on the treatment of this aggressive neoplasm. Most of them use a multimodality approach involving surgery, anthracycline-based combination chemotherapy, prophylactic intrathecal chemotherapy and cranial/scrotal irradiation. This study has been done to review the clinical, pathological profile and treatment outcome of DLBCL testis at our centre in southern India.

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MATERIALS AND METHODS

We retrospectively reviewed 286 registered cases at our institute, aged >14 years, diagnosed as DLBCL by appropriate tissue/lymph node biopsy confirmed by immunohistochemistry (WHO classification) between January 2007 and December 2011. Of these patients, those with primary involvement of the testis with or without regional lymph nodes were included in the study. The demographic details, clinical details, investigations, treatment and outcome were recorded and analysed.** Cotswold's modification of Ann-Arbor staging was used and International prognostic scoring (IPI) was done. Response was assessed according to standard criteria. Overall survival (OS) was calculated from the date of diagnosis until death (all causes) or last follow-up. Patients were followed-up every 3 months for 2 years and 6 months thereafter. Patients were considered on continuous follow-up if the last visit was within 6 months of data censoring.

RESULTS

Median age was 58 (46-76) years [Table 1]. Six patients had right testis and three had left testis involvement. All presented with testicular swelling, two had B symptoms and three had abdominal lymphadenopathy. None had Bone marrow or CNS involvement. CD 20 monoclonal antibody was positive in all

the patients. Three patients were in low-intermediate and six were in low IPI score. One patient was lost to follow up without treatment. All patients underwent high inguinal orchiectomy. Eight cases received anthracycline-based chemotherapy and six completed three or more cycles. All the patients tolerated chemotherapy without any grade III/IV toxicity. Four patients achieved complete response. Among these, one had nodal relapse at 42 months (died of disease), one was lost to follow up with no disease, and two had CNS relapse at 32 (lost to follow up with disease) and 70 months (alive with disease). Two had progressive disease (one alive with disease and one died of disease). The complete follow up was available from five patients with a median OS of 36 months (11-78 months).

DISCUSSION

DLBCL is the most common PTL and constitutes around 69-75% of PTL.^[2,4,6-8] The age at presentation is usually beyond the sixth decade of life. The median age of presentation in our study (58 years) was on par with other Indian study, but early when compared to studies from other countries (70 years).^[4,6-9] Primary DLBCL of testis usually presents with an insidious onset of unilateral painless enlargement of testis. Thirty to forty percent of the patients may present with a hydrocele and shooting pain due to epididymo-orchitis. There is a propensity to involve the

Table 1: Showing characteristics of all the patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age in years	46	54	55	55	58	62	70	74	76
B symptoms	Yes	Yes	No	No	No	No	No	No	No
ECOG PS	1	1	1	1	1	1	1	2	1
Abdominal Lymph node	No	No	No	No	Yes	Yes	Yes	No	No
Elevated LDH	Yes	No	Yes	No	Yes	Yes	Yes	No	No
Ann-Arbor Stage	IE	IE	IE	IE	IIE	IIE	IIE	IE	IE
IPI score	1	0	1	0	1	2	2	2	1
CSF/CNS involvement	No	No	No	No	No	No	No	No	No
IHC	CD20+, CD30-, LCA+, CD 3-	CD20+, CD30-, LCA+	CD20+, CD30-, LCA+	CD20+, CD30-, LCA+	CD20+, CD30-, LCA+, CD 3-	CD20+, CD30-, CD 3-	CD20+, CD30-, LCA+, BCL 2+	CD20+, CD3-, LCA+	CD20+, CD30-, LCA+
Surgery	Orchiectomy	Orchiectomy	Orchiectomy	Orchiectomy	Orchiectomy	Orchiectomy	Orchiectomy	Orchiectomy	Orchiectomy
Chemotherapy x cycles	CHOP x 6	CHOP x 6	CEOP x 6	-	CHOP x 1+G-CSF	CHOP x 2	COP x 6	CEOP x 3	CEOP x 6+G-CSF
Radiotherapy	No	No	No	-	No	No	No	No	No
Response	CR	CR	PD	-	-	-	PD	CR	CR
Follow up	Nodal Relapse after 42m-Died of Disease	CNS relapse after 32m- lost With Disease	Alive with disease	Lost	Lost	Lost	Died of Disease	Lost - No disease	CNS relapse after 70 m- Alive
OS	56 m	36 m	12 m	-	-	-	11 m	2 m	78 m

CHOP: Cyclophosphamide 750 mg/m², doxorubicin 50mg/m², vincristine 1.4 mg/m² and prednisone 100 mg/d for 5 days, every 21 days,

CEOP: Cyclophosphamide 750 mg/m², epirubicin 60 mg/m², vincristine 1.4 mg/m² and prednisone 100 mg/d for 5 days, every 21 days,

CNS: Central nervous system, CR: Complete response, CSF: Cerebrospinal fluid, ECOG PS: Eastern cooperative oncology group performance status,

G-CSF: Granulocyte colony stimulating factor, IHC: Immunohistochemistry, IPI: International prognostic index, LDH: Lactate dehydrogenase,

M: Months, OS: Overall survival, PD: Progressive disease

opposite testis which can be synchronous or metachronous. B symptoms may be present in upto one-third.^[4,7] All the patients in our series were presented with painless unilateral testicular enlargement and two had B symptoms. None had involvement of the opposite testis or presented with epididymo-orchitis/hydrocele. Three had retroperitoneal lymph node involvement at presentation.

There is a propensity for involvement of certain extranodal sites especially contra lateral testis, the waldeyer ring, skin, lung, and CNS.^[3,4] None of the patients in our series had involvement of these sites.

Several variables have been reported as prognostic factors of PTL: Age, B symptoms, performance status (PS), tumour size >9 cm, spermatic cord involvement, elevated LDH, histologic grade, vascular invasion, CNS involvement, Ann-Arbor stage and IPI score.^[1,7,10,11] In our study, median age was 58 years, all were in good ECOG performance status except one (PS 2), two had B symptoms, IPI score was 2 in three cases, 1 in four cases and 0 in two cases. None had CSF or CNS involvement. All our patients were in either stage I or II, which is similar to other studies.^[1,12,13]

In view of small retrospective case series and lack of clinical trials, the treatment of testicular lymphoma has remained a matter of intense discussion and controversy.^[2,4,7] The treatment can be broadly divided into limited (stage I and II) and advanced stage (stage III and IV). The largest retrospective series [Table 2] of testicular DLBCL patients between 1968 and 1998 was reported by the International Extra nodal Lymphoma Study Group (IELSG).^[7] This study emphasized the high risk of relapse and poor outcome in patients with intermediate to high IPI score, in the absence of prophylactic

radiation to the contralateral testis, and treatment with non-anthracycline-based chemotherapy.^[7] Another recent study concluded that only poor ECOG performance status, infiltration of adjacent tissues, and bulky disease as independent prognostic factors.^[17] Earlier with high inguinal orchiectomy alone, OS was 10% at 5 years in stage I primary DLBCL of testis due to dissemination of the disease.^[12,18] Several Studies showed that addition of anthracycline-based chemotherapy and radiation therapy lead to improvement in outcome and survival.^[13,19] In spite of multimodality therapy, prognosis of this entity is poor with relapse in nearly half the patients and CNS relapse in 15-20% at 5 years.^[1,18]

The CHOP [Table 1] regimen has been the mainstay of therapy for several decades. Role of rituximab in improving OS is rather controversial in PTL and some authors attribute this improvement in prognosis over the last decade to the use of multimodality therapy, cranial irradiation and intrathecal methotrexate. Earlier, one study showed that the addition of rituximab to anthracycline-based chemotherapy improved outcome in stage I and II PTL.^[20] But in another study, the addition of rituximab to chemotherapy did not prolong the survival of primary testicular DLBCLs.^[17]

CNS relapse remains a major problem; hence, routine CNS prophylaxis is recommended. Over the last two decades, various modalities have been tried including prophylactic cranial irradiation, intrathecal methotrexate and chemotherapy to reduce CNS relapse. Ostronoff *et al.*,^[21] concluded that all patients with testicular lymphoma should undergo CNS prophylaxis as mentioned above. However, there is no consensus so far on the management/prevention of CNS relapse. One study also emphasized the role of irradiation to contralateral testis as it improved the progression free survival by 34% and OS by 28%.^[7]

Table 2: Summarizing the review of literature with special reference to histology, treatment and outcome

Study/year	Number and duration of study	Histology	Treatment	CNS prophylaxis	Outcome
Wang <i>et al.</i> , ^[4] 2013	2001-2012 n=13 PTL-13 DLBCL-9	DLBCL/NHL B cell type/T cell type	Orchiectomy- all RT- 1 CT- 4	3	PFS - 22.57 months
Gupta <i>et al.</i> , ^[8] 2009	2002-2008 n=6 PTL-6 DLBCL-5	DLBCL/NHL	Orchiectomy- 4 RT-1 CT-6	3- Prophylactic cranial RT IT MTX-6	Median PFS- 42 months
Lantz AG <i>et al.</i> , ^[14]	1992-2005 n=12 DLBCL-11 ALCL-1	DLBCL/ALCL	Orchiectomy- all, RT-7 CT- 7	IT MTX-3 Cranial RT-1 Scrotal RT-5	Median OS - 29 m
Darby <i>et al.</i> , ^[15] 2005	1972-2002 n=30	NHL	Orchiectomy- all RT- 7, CT- 15	None	Relapse after CR: 40%; Median time of relapse 9 months
Vitolo <i>et al.</i> , ^[11] 2011	Phase II trial 2001-2006 n=53	Stage I or II PTL	Orchiectomy- all RT- 47 CT- all (R- CHOP21)	50	5-year PFS and OS 74% and 85%.
Reyes <i>et al.</i> , ^[16] 2005	Prospective randomized trial. n=630	Stage I or II aggressive lymphoma (DLBCL)	Arm 1: 3×CHOP+RT (n=321) Arm 2: 3×ACVBP (n=309)	-	OS- 5-year Arm 1: 81% Arm 2: 90% (P<0.001) EFS- 5-year Arm 1: 74% Arm 2: 82% (P<0.001)
Present study 2013	2007-2011 n=9	DLBCL	Orchiectomy- 9, RT- 0 CT- 6	No	Median OS- 24 months

ACVBP: Doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, ALCL: Anaplastic large cell lymphoma, CT: Chemotherapy, CR: Complete remission, DLBCL: Diffuse large B cell lymphoma, EFS: Event free survival, IT MTX: Intrathecal methotrexate, N: Number, NHL: Non-Hodgkin's lymphoma, PFS: Progression free survival, OS: Overall survival, PTL: Primary testicular lymphoma, RT: Radiotherapy, R-CHOP: Rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone

In our study, no patient received rituximab in view of financial constraints. Earlier, the role of CNS prophylaxis was controversial as intrathecal therapy does not eliminate CNS relapses; relapses have been observed even after intrathecal therapy and also occur in brain parenchyma.^[7] So our patients did not receive it, but it has been incorporated into our present protocol following these relapses.

A recent phase II trial concluded that combined treatment with rituximab with CHOP, intrathecal methotrexate, and testicular radiotherapy (reduce contralateral testis relapses) is feasible in patients younger than age 80 years and associated with a good outcome in patients with PTL.^[1] However, a longer follow-up is needed to clarify the role of rituximab in PTL. An ongoing prospective study (IELSG-30) will answer the role of intrathecal liposomal cytarabine and systemic intermediate dose methotrexate.

Given the lack of randomized data in this rare disease, treatment options are based only on data available from small retrospective studies. The prognosis remains very poor despite combined modality treatment following orchiectomy. Treatment of relapses at extranodal sites, contralateral testis, and/or CNS needs to be further investigated using new molecular approaches and/or more aggressive management.

To conclude, the PTL is a rare disease and needs high index of suspicion for early diagnosis. Multimodality therapy is recommended for the treatment of stage I-II PTL, which consists of orchiectomy, four to six cycles of anthracycline-based combination chemotherapy with rituximab, radiation to involved lymph nodes and contralateral testis, and CNS prophylaxis. The outcome needs to be further investigated using biological approaches (Rituximab) and/or more aggressive management.

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REFERENCES

1. Vitolo U, Chiappella A, Ferreri AJ, Martelli M, Baldi I, Balzarotti M, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab- CHOP, CNS prophylaxis, and contralateral testis irradiation: Final results of an international phase II trial. *J Clin Oncol* 2011;29:2766-72.
2. Gundrum JD, Mathiason MA, Moore DB, Go RS. Primary testicular diffuse large B-cell lymphoma: A population-based study on the incidence, natural history, and survival comparison with primary nodal counterpart before and

- after the introduction of rituximab. *J Clin Oncol* 2009;27:5227-32.
3. Fonseca R, Habermann TM, Colgan JP, O'Neill BP, White WL, Witzig TE, et al. Testicular lymphoma is associated with a high incidence of extranodal recurrence. *Cancer* 2000;88:154-61.
4. Wang C, Wang H, Wang Q, Shi B. Primary testicular lymphoma: Experience with 13 cases and literature review. *Int J Hematol* 2013;97:240-5.
5. Shahab N, Doll DC. Testicular lymphoma. *Semin Oncol* 1999;26:259-69.
6. Miedler JD, MacLennan GT. Primary testicular lymphoma. *J Urol* 2007;178:2645.
7. Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. *J Clin Oncol* 2003;21:20-7.
8. Gupta D, Sharma A, Raina V, Bakhshi S, Mohanti BK. Primary testicular non-Hodgkin lymphoma: A single institution experience from India. *Indian J Cancer* 2009;46:46-9.
9. Ahmad SS, Idris SF, Follows GA, Williams MV. Primary testicular lymphoma. *Clin Oncol* 2012;24:358-65.
10. Cao B, Ji DM, Zhou XY, Zhao TP, Guo Y, Wang ZH, et al. A clinical analysis of primary testicular diffuse large B-cell lymphoma in China. *Hematology* 2011;16:291-7.
11. Mazloom A, Fowler N, Medeiros LJ. Outcome of patients with diffuse large B-cell lymphoma of the testis by era of treatment: The M. D. Anderson Cancer Center experience. *Leuk Lymphoma* 2010;51:1217-24.
12. Zouhair A, Herrmann E, Ugurluer G, Gaye PM, Mirimanoff RO, Ozsahin M. Primary testicular lymphoma. *Swiss Med Wkly* 2010;140:13076.
13. Touroutoglou N, Dimopoulos MA, Younes A, Hess M, Pugh W, Cox J, et al. Testicular lymphoma: Late relapses and poor outcome despite doxorubicin-based therapy. *J Clin Oncol* 1995;13:1361-7.
14. Lantz AG, Power N, Hutton B, Gupta R. Malignant lymphoma of the testis: A study of 12 cases. *Can Urol Assoc J* 2009;3:393-8.
15. Darby S, Hancock BW. Localised non-Hodgkin's lymphoma of the testis: The Sheffield lymphoma group experience. *Int J Oncol* 2005;26:1093-9.
16. Reyes F, Lepage E, Ganem G, Molina TJ, Brice P, Coiffier, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med* 2005;352:1197-205.
17. Wang Y, Li ZM, Huang JJ, Xia Y, Li H, Li YJ, et al. Three prognostic factors influence clinical outcomes of primary testicular lymphoma. *Tumour Biol* 2013;34:55-63.
18. Moller MB, d'Amore F, Christensen BE. Testicular lymphoma: A population-based study of incidence, clinicopathological correlations and prognosis. The Danish Lymphoma Study Group, LYFO. *Eur J Cancer* 1994;30:1760-4.
19. Vural F, Cagiran S, Saydam G, Hekimgil M, Soyer NA, Tombuloglu M, et al. Primary testicular lymphoma. *J Natl Med Assoc* 2007;99:1277-82.
20. Aviles A, Nambo MJ, Cleto S, Neri N, Huerta-Guzman J. Rituximab and dose-dense chemotherapy in primary testicular lymphoma. *Clin Lymphoma Myeloma* 2009;9:386-9.
21. Ostronoff M, Soussain C, Zambon E, Moran A, Droz JP, Bosq J, et al. Localized stage non-Hodgkin's lymphoma of the testis: A retrospective study of 16 cases. *Nouv Rev Fr Hematol* 1995;37:267-72.

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