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Primary Testicular Lymphoma: A Study of 11 Cases

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Authors' contributions

This work was carried out in collaboration between all authors. Author HR designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors NBS, YBY, BA, SH, HEO, AK managed the literature searches, analyses of the study performed the spectroscopy analysis. All authors read and approved the final manuscript.

Mini-review Article

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ABSTRACT

Primary testicular lymphoma (PTL) is an uncommon extranodal presentation constituting 1% of all NHL and 5% of all testicular neoplasm. The objective of our study was to identify the presenting signs and symptoms, treatment and outcome of patients with testicular lymphoma diagnosed at the Hematology department of Farhat Hached University Hospital from 1997 to 2007 and to perform bibliography review about this pathology.
Eleven cases were identified; the median age was 61 years (range:31-83). All patients presented with testicular and scrotal swelling or mass. B symptoms (recurrent fever of>38ºC temperature, night sweets and unexplained weight loss of>10% of the body weight within six months prior to diagnosis) were present in 6 patients. According to the "Ann-Arbor staging system", 7 patients were classified stage IE(involving a single lymph node region (I) or single extralymphatic organ or site) and IIE (two or more involved lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site), 4 patients were classified stage IVE (the presence of diffuse or disseminated involvement of one or more extralymphatic organs (e.g., liver, bone, marrow, lung), with or without associated lymph node involvement). International Prognostic index was low (<2) in 7 patients and high (≥2) in 4 cases. Orchidectomy was performed in all cases. Eight patients received chemotherapy based on COP (2cases),

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mini CEOP (3 cases), ACVBP (2 cases). Eight patients received central nervous system prophylaxis in the form of intrathecal methotrexate. Radiation at the dose of 40Gy was given to 3 patients. Three patients achieved complete remission. Two patients relapsed. The median survival was 3 months (range: 1 week-107 months).
Testicular lymphoma is a rare and deadly form of extra nodal lymphoma, randomized prospective treatment trials may help to establish better treatment strategies.

Keywords: Primary testicular lymphoma; treatment; prognosis; outcome.

1. INTRODUCTION

Primary testicular lymphoma (PTL) is an uncommon extra nodal presentation, representing 1 to 2% of all non Hodgkin lymphoma (NHLs) and approximately 5% of all testicular neoplasms [1]. The disease typically presents in patients older than 60 years, right and left sided testicular involvements are equal in frequency. The diagnosis is usually obtained after orchidectomy [2], and the dominant histological subtype is diffuse large B-cell lymphoma (DLBCL) [3].

The prognosis is poor after surgery alone and addition of post operative radiotherapy improves 5 years survival up to 50-60% [4].

Chemotherapy with anthracycline is the recommended regimen, achieved by orchidectomy and combined radiotherapy. PTL has shown tendencies to relapse in central nervous system (CNS), controlateral testis and less commonly lung, skin, bone, adrenal glands, liver, gastrointestinal tract and nodal sites [4].

In this retrospective study we aimed to evaluate the clinical characteristics of primary testis lymphoma and effectiveness of the treatment modality in our department.

2. PATIENTS AND METHODS

Between June 1997and August 2007 we evaluated clinical features, management, outcome and survival of 11 adult male patients with PTL presented to the department of Haematology of Farhat Hached University Hospital.

We used data from the available clinical files concerning patients' age, symptoms, disease extension, histopathological subtype according to the world health organisation (WHO), level of lactate dehydrogenase (LDH) at presentation, treatment modalities, response rate, relapse pattern, and survival time.

Pre-treatment staging evaluation consisted of a medical history, physical examination, laboratory investigation of LDH level, computed tomography (CT) scan of the neck, thorax and abdomen, and a staging bone marrow (BM) biopsy. During the treatment period all patients were re-evaluated at the third or fourth cycles of chemotherapy for the signs of disease or any additional new involvement site for the progressive disease.

The clinical stage of the disease was designated by the Ann Arbor classification (Table 1).

B symptoms were defined as a recurrent fever of>38ºC temperature, night sweets and unexplained weight loss of >10% of the body weight within six months prior to diagnosis. Patients were retrospectively classified into four risk groups according to an International Prognostic Index (IPI) score (Table2): low (IPI score of 0-1), low intermediate (IPI score of 2), high intermediate (IPI score of 3), high risk (IPI score of 4-5).

Table 1. Ann Arbor staging system

Stage description	
I	Involving a single lymph node region (I) or single extralymphatic organ or site (IE)
II	Two or more involved lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Lymph node involvement on both sides of the diaphragm (III), or localized involvement of an extralymphatic organ or site (stage IIIE), or spleen (IIIS), or both (IIIES)
IV	The presence of diffuse or disseminated involvement of one or more extralymphatic organs (e.g., liver, bone, marrow, lung), with or without associated lymph node involvement

The presence or absence of systemic symptoms should be noted with each designation: A for asymptomatic, B for presence of fever, sweats or weight loss >10% of body weight

Table 2. International prognostic index

Parameters	0	1
Age years	60	>60
Performance status	0 or 1	2-4
Stage	I or II	III or IV
Serum LDH	1xnormal	>1xnormal

All patients had a diagnosis of lymphoma by orchidectomy. Complete remission was defined as absence of disease signs and symptoms one month after the completion of treatment.Relapse was defined as the appearance of a new lesion for patients in complete remission. Overall survival was calculated from time of diagnosis to time of death or last follow- up.

2.1 Statistics

Survival analysis and life table were completed using the Kaplan-Meier method .Patients definitive clinical and demographic properties were analysed by computerized method using SPSS for windows.

3. RESULTS

Patient characteristics are listed in (Table 3).

Table 3. Clinical features at diagnosis, treatment and outcome of the patients

Patient	Age	testis	stage	B symptoms	LDH level	Additional extranodal site	IPI	Histology	Diagnostic procedure	Initial treatment	CNS prophylaxis	RT	Relapse site	Result
1	64	L	IE	-	elevated	-	1	DLBCL	orchidectomy	3 CEOP	+	+	-	CR
2	46	R	II	-	elevated	-	1	DLBCL	orchidectomy	ACVBPX4+MTXX2+holoxan+VP16X3+cytosineX2	+	-	-	D
3	61	R	IV	+	elevated	Lung+ adrenal glands	3	DLBCL	orchidectomy	CHOPX8	+	-	CNS+surrenal	CR,D
4	35	L	I	-	N	-	0	DLBCL	orchidectomy	CHOPX3	-	+	-	CR
5	61	L	I	-	N	-	1	DLBCL	orchidectomy	CHOPX3	-	+	+CNS	D
6	31	L	IV	+	elevated	Bone morraw extention	3	DLBCL	orchidectomy	-	-	-	-	D
7	40	R	IV	+	elevated	lung	2	Tlympho-ma	orchidectomy	-	-	-	-	D
8	73	R	IV	+	elevated	Bone morraw extention	3	DLBCL	orchidectomy	COPX3	-	-	-	D
9	79	R	I	-	N	-	1	DLBCL	orchidectomy	ACVBPX4	-	-	-	lost of view
10	66	R	II	+	N	-	1	DLBCL	orchidectomy	COPX3	-	-	-	D
11	83	R	I	-	N	-	1	DLBCL	orchidectomy	-	-	-	-	

L: left, R: right, N: normal, CR: complete remission, D: dead, COP (cyclophosphamide 300mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1 and prednisolone 60mg/m^{2}days 1-5) CHOP (cyclophosphamide 750mg/m^2 day 1, doxorubicin 50mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1 and prednisolone 100mg /m^{2}days 1-5) ACVBP (doxorubicin 75mg/m^2 day1, cy 1200mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1and 5, bleomycin 10mg/m^2 and prednisolone 60mg/m^2 days 1-5) mini-CEOP(epirubicine 35mg/m^2 day 1, cy 500mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1 and prednisolone 60mg/m^2 days 1-5) DLBCL:Diffuse large Bcell lymphoma

Eleven patients with a median age of 61 years (range: 31-83), at presentation were included in the study. The majority of patients were histologically diagnosed as DLBCL except one patient who was diagnosed as peripheral T cell lymphoma. All the patients admitted with a complaint painless testicular swelling, four patients had involvement of the left testis, seven of the right and six patients had B symptoms. Seven patients were Ann Arbor stage IE and IIE, the others were stage IVE. Bone marrow involvement of lymphoma was present in 2 patients, two patients had additional extra nodal lymphoma involvement at the time of diagnosis, with infiltration of the lung in two cases, and adrenal gland involvement in one case (Fig.1A).

Five patients presented with high serum LDH levels .According to the IPI score seven patients had low risk disease, and four high risk disease.

3.1 Treatment

All patients underwent orchidectomy. Only 8 patients received chemotherapy based on COP (cyclophosphamide (cy) 300mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1 and prednisolone 60 mg/m^2days 1-5) in 2 cases, CHOP (cy 750mg/m^2 day 1, doxorubicin 50mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1 and prednisolone 100mg days 1-5) in 3 cases.

ACVBP(doxorubicin 75mg/m^2 day1, cy 1200mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1and 5, bleomycin 10mg/m^2 day 1and 5 and prednisolone 60mg/m^2 days 1-5) in 2 cases ,and mini-CEOP(epirubicine 35mg/m^2 day 1, cy 500mg/m^2 day 1, vincristine 1.4mg/m^2 but not more than 2.0mg day 1 and prednisolone 60mg/m^2 days 1-5) in 1 case.
Eight patients received central nervous system prophylaxis in the form of intrathecal methotrexate (IT MTX).Radiation therapy was given to 3 patients: 1 cranial, 3 to the scrotum and ipsilateral/para-aortic lymph node at the dose of 40 grays. Patients were not been treated in the same manner due to the time difference of application and clinical protocols.
Outcome: Complete remission was achieved in 3 patients: 2 of them relapsed, they presented with CNS involvement (Fig.1B). 6 patients died from disease progression and one died from a secondary neoplasia (adenocarcinoma of the lung) 6 years after the diagnosis of testicular lymphoma.Median survival was 3 months (one week-107 months).The 5-year overall survival was 30 %."(Fig. 2)". At the time of writing all patients was died.

4. DISCUSSION

Primary testicular lymphoma is predominantly a disease of the elderly, the median age in our study is 61 years which is comparable to other reports [5-9]. It can exceptionally occur in young adults [10,11].

In our patients the first symptom of the testis lymphoma was painless, testicular swelling and diagnosis was generally performed by orchidectomy.Histological diagnosis showed the dominance of B-cell type and the major lymphoma subtype was DLBCL [12,13], ten of our patients had DLBC histology. The risk of controlateral testicular relapse is known to be high. The first diagnosis and therapeutic procedure performed in testicular lymphoma case is orchidectomy [14], which was performed in all of our patients.

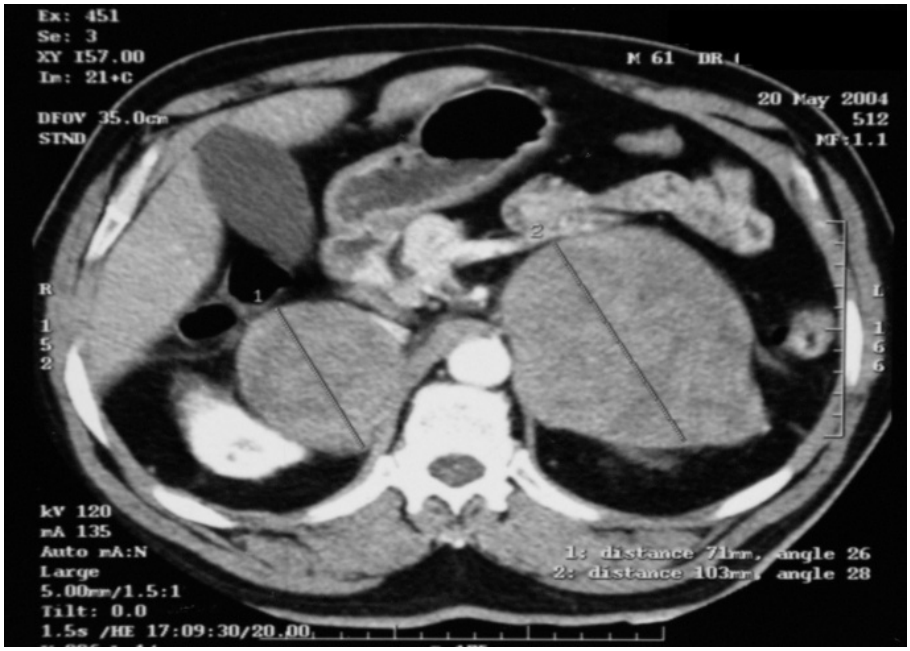

Fig. 1A. Computed tomography with injection demonstrating bilateral infiltration of adrenal glands (patient 3)

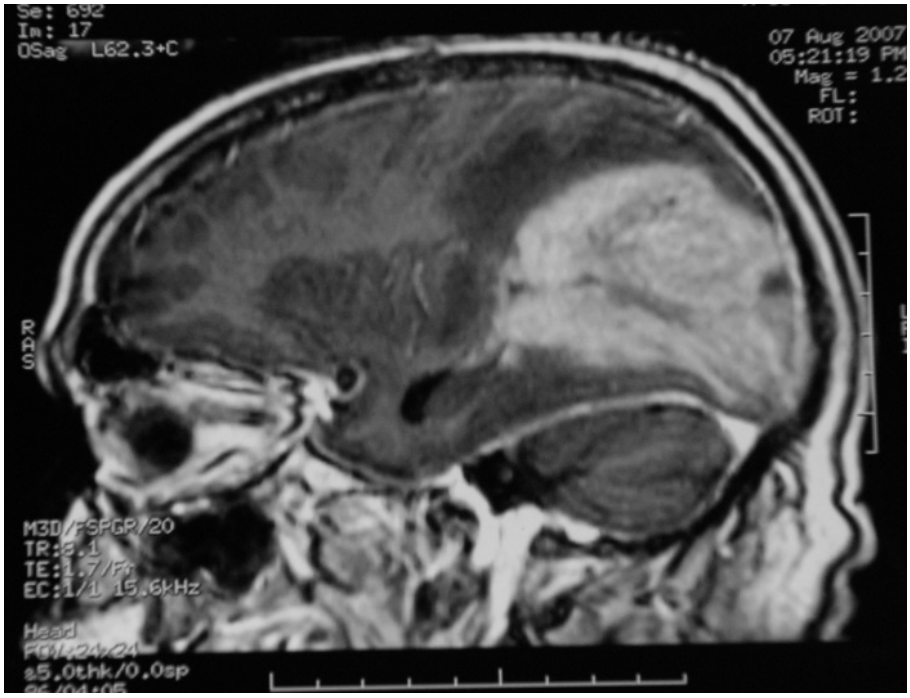

Fig. 1B. MRI (Sagital) T1weighted after Gadolinium injection: Brain involvement in the occipital area (patient 3)

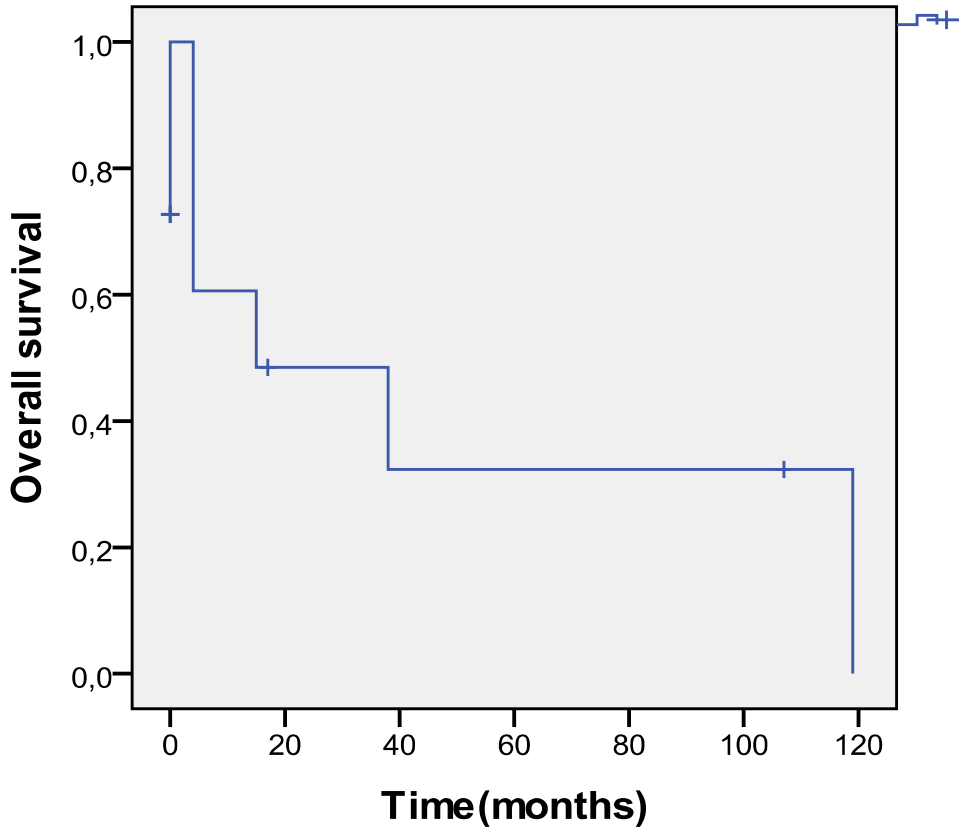

Fig. 2. Overall survival curve

Post operative radiotherapy was introduced in the 1980's by Duncan et al, resulting in 5 year survival rates of 64% in stage I/II and 17% in stage III/IV [8], 3 of our patients received radiotherapy. In another study, CR rate of 100%, 5 years survival rate of 93% were reported with anthracycline based chemotherapy and radiotherapy in stage IE and IIE patients [15]. We have used anthracycline based chemotherapy in 6 of our patients. CNS relapse is considered to be common, but whether prophylactic CNS directed therapy prevents relapse has not been consistently reported [16].

In our study, relapse was seen in two patients with involvement of the brain despite CNS prophylaxis in one of them.

Outcome of patients presenting with advanced stage testicular lymphoma is dismal, our experience with such patient is very similar to that reported by Touroutoglou et al. [17] and Crellin et al. [8]. Median survival for our patients was between one week and 107 months. Our study confirmed the poor prognosis of primary testicular lymphoma for both early and advanced stage disease.

5. CONCLUSION

Testicular lymphoma represents an entity that should be considered for differential diagnosis with other testicular malignancies. The results of this retrospective survey confirmed that

PTL is a very rare lymphoma, and it is characterized by a very bad prognosis. The treatment recommendation was recently changed to a combined modality of systemic doxorubicin based chemotherapy, prophylactic IT chemotherapy, and scrotal radiotherapy [9]. Due to the rarity of the disease a standardized therapeutic approach is lacking, prospective data on larger series of patients treated homogeneously also with innovative approaches is needed in order to establish the best treatment for this aggressive lymphoma.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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