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Testicular lymphoma - An easily underestimated malignancy in geriatric patients

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Abstract

Background: To evaluate the clinical features and outcomes of testicular lymphoma for patients receiving unilateral orchiectomy following by chemotherapy and radiotherapy at our hospital.

Material and Method: Between January 2005 to September 2019, a total of eight patients with testicular lymphoma underwent unilateral radical orchiectomy were enrolled in this study. All patients received chemotherapy or radiotherapy after operation. The clinical outcome of these patients was evaluated by retrospective chart review.

Results: Of the eight patients, seven patients (87.5%) had primary diffuse large B cell lymphoma (DLBCL), while the other 1 patient was reported as NK/T-cell lymphoma. The average age of the patients was 68.9-year-old. One patient was lost to follow-up after surgery. The average follow-up duration was 7.8 months. The average progression free follow-up duration was 3.5 months. Six patients were Ann Arbor stage I or II at diagnosis and two were stage III or IV. The mean IPI score at diagnosis was 2.1. For seven patients with DLBCL, two patients received chemotherapy with regimen of rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride (R-EPOCH). One patient received R-EPOCH and regional radiotherapy. Three patients received chemotherapy with regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone for 14 days. None of patient received prophylactic intrathecal chemotherapy. Complete remission was only achieved in one patient. Two patients were still undergoing chemotherapy during the last follow-up and had no sign of relapse. Partial remission was noted in four patients, but all of them still died of disease during follow-up.

Two patients died due to their underlying disease. One was lung cancer stage IV, and the other was HCC stage IV. Two patients died due to lymphoma, and both cases showed relapse in brain before death.

Conclusions: Testicular lymphoma is highly malignant and with high metastatic potential. Once underestimation or misdiagnosis occurs, it may come out to be social-legal issue. Thus, it should be highly alerted once if unilateral painless testicular mass detected in geriatric patients. Radical orchiectomy stands as gold standard for testicular lymphoma, while local radiotherapy, chemotherapy and immunotherapy also played an important role in treatment.

Keywords: Testicular lymphoma; Large B-cell lymphoma; Orchiectomy.

Introduction

Testicular tumor is a common disease in urological department. Germ cell tumor is reported gaining a higher incidence in child and adolescent, while lymphoma represents in most cases in people with age > 60-year-old [1]. Histologically, the most common subtype of testicular lymphoma is diffuse large B-cell lymphoma (DLBCL), representing 80-90% of diagnosed tumors. Such disease has a tendency to disseminate to extra-nodal organ, including lung, skin, pleura, kidney, Waldeyer's ring, especially contralateral testis and central nerve system (CNS) [2,3]. Testicular natural killer/T-cell lymphoma may also be associated with Epstein-Barr (EB) virus infection [4,5]. Treatment of testicular lymphoma includes radical orchiectomy, local radiotherapy, systemic chemotherapy with doxorubicin-based regimen, and target therapy with Rituximab [6,7,8].

In this retrospective study, 8 cases with testicular tumor in our hospital were evaluated the clinical and pathological characteristics. Literature was reviewed with the aim of expanding our understanding of this rare and deadly malignancy.

Patients population and method

Patients: Under the permission of our internal review board, medical record of patients with testicular tumor at Ditmanson Medical Foundation Chia-yi Christian Hospital from 2005 to 2019 was reviewed retrospectively. Eight patients with testicular lymphoma diagnosed in our hospital were enrolled in this study.

Diagnosis: All patients underwent unilateral radical orchiectomy for palpable testicular mass, and the diagnosis of testicular lymphoma is based on the pathology finding. Among the eight patients reported as lymphoma, seven patients had diffuse large B lymphoma (DLBCL), and the other one patient had extranodal NK/T-cell lymphoma.

Ann Arbor classification system was used as staging evaluation of diffuse large B cell lymphoma and NK/T-cell lymphoma. Stage I of disease was described as single lymphatic organ or extranodal site. Stage II of disease was described as two or more lymphatic regions on the same side of the diaphragm, or a single extranodal organ plus lymph node involvement on the same side of the diaphragm. Stage I of disease was described as regional lymph nodes involved. Stage II of disease was described as distant lymph nodes involved. Stage III of disease was described as lymph node involvement detected on both sides of the diaphragm. Stage IV of disease was described as disseminated disease with involvement of other extranodal

sites (i.e., liver, bone marrow, abdominal wall) [9].

International Prognostic Index (IPI score) was used as a prognostic scoring system to evaluate the patients. Prognostic factors included (1) Age > 60 years old (2) Serum LDH > 1*normal level (3) Stage III or IV of lymphoma (4) Extranodal involvement > 1 site. Each prognostic factor gets one point if patient meets such criteria. The result reveals that scoring 0 or 1 has low risk, scoring 2 has low intermediate risk, scoring 3 has high intermediate risk, and scoring 4 or 5 has high risk [9].

Outcome evaluation

The Complete Remission (CR) was clarified as the absence of symptoms and signs of disease 1 month after completion of treatment. The overall survival (OS) was counted from the time of diagnosis to the time of death or the last follow-up. Progression-free survival (PFS) was calculated from the time of diagnosis to the time of treatment failure, relapse, or death from testicular lymphoma. Relapse was categorized as the appearance of a new lesion in a patient who was classified as complete remission [3].

Statistically analysis

The study population was characterized by descriptive analysis. The mean and standard deviation (SD) were described and calculated as continuous variable with normal distribution. The percentage was used in categorical variables. The statistical analyses were calculated by the SPSS Statistics 22.0 software package. (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics of patients: A total of 8 patients with a diagnosis of PTL were initially reviewed in the study. The average age of the patients was 68.9 ± 8.3 years (range 61-91 years). Their clinical characteristics are shown in Table 1 and supplemental Table 2. One patient (patient 8) was lost to follow-up after surgery. The average follow-up duration was 7.8 ± 10.2 months (Range 0-30.5 months). The average progression free follow-up duration was 3.5 ± 8.7 months (Range 0-25 months).

Clinical Presentation

All 8 patients had acute onset with painless testicular swelling before diagnosis. Five patients had right testicle involvement, and three patients had left testicle involvement. There was no bilateral testicles involvement case in this study.

Patients had normal alpha-fetoprotein (AFP) levels (1.4-3.5 ng/ml; normal range, 0-20 ng/ml). The other one patient had a higher AFP level 19.1 ng/ml, but this may due to his underlying disease of hepatocellular carcinoma. b-Human chorionic gonadotropin (b-HCG) level was measured pre-operatively in all 8 patients, and the result showed all in normal range. (0-1.05 IU/L; normal range 0-2.6 IU/L). 6 patients were Ann Arbor stage I or II at diagnosis and two were stage III or IV. The mean IPI score at diagnosis was 2.1 ± 1.2 (range 1-4). Bulky disease was not identified in any of the patients.

Histopathological Features

B-cell lymphoma was confirmed in 7 patients after histopathological examination, and all of them were reported as diffuse large B cell lymphoma; one case was characterized as NK/T-cell lymphoma, but this one was a relapsing case (origin site: NK/T-cell lymphoma, nasal type, right paranasal sinus) Ki-67 expression was determined in specimens from the patients 1, 2, 3, 5 and 6, and was 60%, 80%, 85%, 80%, 80% respectively, indicating high malignancy.

Treatment and Outcome

Orchiectomy was performed in all 8 patients as a diagnostic and initial therapy. For the patient with NK/T-cell lymphoma, he (patient 4) received EPOCH + regional radiotherapy. For patients with diffuse large B cell lymphoma, two patients (patient 5,6) received R-EPOCH chemotherapy. One patient (patient 3) received R-EPOCH+regional radiotherapy. Three patients (patient 1,2, and 7) received R-CHOP-14 (14-day cycle). One patient (patient 8) lost follow-up after operation was performed. None of patient received prophylactic intrathecal chemotherapy. Complete remission was achieved in only one patient in our record (patient 3). Two patients were still undergoing chemotherapy during the last follow-up and had no sign of relapse (patients 1 and 2). Four patients died during follow-up. Two patients died due to their underlying disease. One was lung cancer stage IV (patient 5), and the other was HCC stage IV (patient 6). Two patients died due to lymphoma, and both cases showed relapse in brain before death. The time to relapse was 1.3 and 1.6 months in patient 7 and 4. One patient was lost follow-up after operation.

Table 1: Summary of clinicopathological characteristics, treatment agent, and outcome

Age (years)	68.9 (60.6, 77.2)
Follow-up duration (months)	7.79(-2.38, 17.96)
Location	
Right/Left/Bilateral	5/3/0
Stage	
I/II/III-IV	4/2/2
IPI	
0/1-2/3-4	0/6/2
Histotype	
DLBCL/NK-T cell	7/1
Treatment	
Not yet/R-EPOCH/EPOCH/R-CHOP	2/4/1/1
CNS prophylaxis(Yes/No)	0/8
Replase	2
PFS duration(months)	3.49 (-5.22, 12.21)
Death	4

Data are presented as mean (range) or count. Table includes data of 8 patients. IPI: international prognostic index; PFS: Progression-free survival; DLBCL: Diffuse large B cell lymphoma; NK-T cell: nature killer cell; CNS Central nerve system; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; R-EPOCH: Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

Table 2: Perioperative/Postoperative treatment and evaluation of relapse.

Patient	Age	Histology	Ann Arbor Classification	IPI	OP	Organ involvement	Treatment	Replase	f/u duration (months)	PF duration (months)
1	62	DLBCL	IE	2	Right orchiectomy	None	Not yet	None	1.2	0
2	75	DLBCL	IE	2	Left orchiectomy	None	Not yet	None	3.5	0
3	61	DLBCL	IIE	1	Right orchiectomy	Paraaortic LN	R-EPOCH+R/T	None	30.5	25
4	65	Extranodal NK/T-cell	IVE	4	Right orchiectomy	Right paranasal sinus	EPOCH+R/T	Brain	8.2	1.6
5	63	DLBCL	IE	1	Right orchiectomy	None	R-EPOCH	None	3.6	0
6	91	DLBCL	IIIBEX	4	Left orchiectomy	None	R-EPOCH	None	1.8	0
7	67	DLBCL	IIE	2	Right orchiectomy	None	R-CHOP(14)	Brain	13.5	1.3
8	67	DLBCL	IE	1	Left orchiectomy	None	Loss follow-up	None	0	0

DLBCL: Diffuse large B cell lymphoma; **Extranodal NK:** Extranodal- nature killer cell; **R-EPOCH:** Rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; **IPI:** International Prognostic Index; **f/u duration:** Follow-up duration; **PF duration:** Progression free duration.

Table 3: Clinicopathologic characteristics of testicular lymphoma patients.

Patient	Age	Histology	Staging	size(cm)	AFP (ng/ml)	β-HCG (mIU/ml)	B2M (ng/mL)	LDH (IU/L)	MUM-1	BCL2	BCL6	MYC	CD20	EBER	Ki-67	f/u duration (months)	PF duration (months)
1	62	DLBCL	IE	7.5 x 4.5	3.5	<1	1917	320	(+)	(+)	(+)	(+)	(+)	(-)	60%	1.2	0
2	75	DLBCL	IE	8.0 x 5.0 x 4.0	1.6	<1	2902	313	(+)	(+)	(+)	(+)	strong	(-)	80%	3.5	0
3	61	DLBCL	IIE	3.5 x 3.0 x 3.0	2.5	<1	-	138	N/A	(+)	(+)	N/A	(+)	N/A	85%	30.5	25
4	65	NK/T-cell	IVE	2.5 x 1.4 x 0.5	2.2	<1	-	216	N/A	N/A	N/A	N/A	(+)	(+)	-	8.2	1.6
5	63	DLBCL	IE	9.3 x 4.5 x 4.3	3.5	0	-	189*	N/A	N/A	N/A	N/A	(+)	(-)	80%	3.6	0
6	91	DLBCL	IIIBEX	7.0 cm	1.5	0.87	-	955	N/A	N/A	N/A	N/A	(+)	N/A	80%	1.8	0
7	67	DLBCL	IIE	6.5 x 4.0 x 3.0	19.1	1.05	-	-	N/A	N/A	N/A	N/A	(+)	N/A	-	13.5	1.3
8	67	DLBCL	IE	5.0 x 3.0 x 3.0	1.4	1.01	-	-	N/A	N/A	N/A	N/A	(+)	N/A	-	0	0

Discussion

In traditional textbook, differential diagnosis of unilateral painless testicular tumor including germ cell tumor (GCT) and non-germ cell tumor (NGCT) based on WHO histological classification of testicular tumors. Germ cell tumor can be divided into seminomatous germ cell tumor (SGCT) and non-seminomatous germ cell tumor (NSGCT) [10-13]. Seminomatous germ cell tumor includes seminoma and spermatocytic seminoma. On the other hand, non-seminomatous cell tumor includes embryonal carcinoma, endodermal sinus tumor (or known as yolk sac tumor), choriocarcinoma, teratoma, polyembryoma, gonadoblastoma [10,12]. Non-germ cell tumor includes sex cord-stromal tumor (Mainly Leydig cell tumor and Sertoli cell tumor), Mixed tumor (Gonadoblastoma), Miscellaneous tumors, Haematolymphoid tumors and Tumors of collecting duct and rete testis [11,13].

Diagnostic criteria includes image study, such as testicular ultrasound, computed tomography (CT), magnetic resonance image (MRI), and lab data of lactate dehydrogenase (LDH), beta-human chorionic

gonadotropin (β-hCG), and alpha-fetoprotein (AFP) [13,14]. It is well known that Germ cell tumor has an overall incidence of 90% in all testicular tumor [13]. However, when looking into elderly group, we are amazed to find out that the answer is not what we have learned before! In out report, eight male patients > 60-year-old with unilateral testicular tumor were diagnosed as lymphoma after operation. Seven of the patients were diagnosed as diffuse large B cell lymphoma, which stands for an incidence rate of 87.5% of diffuse large B cell lymphoma. The other one was diagnosed as metastatic NK-T cell lymphoma.

Unilateral testicular tumor in elderly has a high prevalence of lymphoma, especially diffuse large B cell lymphoma (DLBCL) in recent case reports [14,15]. In Wang et al., another case series, 13 patients > 60-year-old were reported to have unilateral testicular tumor in the beginning. Final pathology showed lymphoma in all these 13 cases. 9 patients were diagnosed as DLBCL (69.2%). 3 patients were diagnosed as non-Hodgkin lymphoma (NHL) with subtype of B-cell type. 1 patient was diagnosed as NHL with subtype of T-1 cell type. All of the patients underwent chemotherapy. Six of them reached complete remission. Three patients had recurrence in the CNS, the epiglottis, and the nasal cavity [14].

The guideline of National Comprehensive Cancer Network in version of 2020 suggests that treatment of monoclonal antibody (Rituximab) plus chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) as R-CHOP stands for the first-line treatment for DLBCL [16]. Operation for cytoreduction is also suggested if solid organ lymphoma such as testicular tumor and mediastinal tumor is diagnosed [13-16]. Combination of local irradiation may be considered in groups of positive regional lymph involvement or invasive subtype of lymphoma [16]. In our report, patient 3, 5, 6 received R-EPOCH (Rituximab plus Etoposide, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) during 2012 to 2017. However, treatment of R-CHOP showed better overall survival (OS) curve and longer free-relapsing survival (FRS) duration in recent years. By far, first line treatment has been standardized with R-CHOP therapy with optional local irradiation in selected cases. Cytoreductive operation is suggested in solid organ involvement. Much more cases of unilateral testicular tumor in elderly have been reported in recent years [16-18].

Such cases may be mis-diagnosed as chronic orchitis or epididymitis [1,2,3,19]. In our report, patient 1 and 2 went to local medical doctor (LMD) firstly. They went to our outpatient department due to persisted symptom even medication has been given at clinics. It should be highly alerted due to potential delayed diagnosis and treatment, which may lead to be ethical or legal problem. We sincerely suggest that unilateral testicular tumor in elderly should be a formal topic of Geriatrics & Gerontology, and guideline for such disease should be established as soon as possible due to progressively aging society.

Conclusion

Testicular lymphoma is not a common geriatric testicular malignancy, which could be easily underestimated and misdiagnosed. Unilateral painless testicular swelling is the most common symptom at first sight, which may be confused with orchitis or the other testicular tumors. Such disease is highly malignant and with high metastatic potential, and should be treated at once if diagnosed. However, it is easy to be underestimated and misdiagnosed if there is only hint of unilateral painless testicular swelling. Once unde-

restimation or misdiagnosis occurs, it may come out to be social-legal issue. Thus, it should be highly alerted once if unilateral painless testicular mass detected in geriatric patients. Gold standard of treatment was still orchiectomy. Study of brain CT and contralateral testicular sonography were recommended due to high metastatic rate.

Internal medical treatment for testicular lymphoma contain chemotherapy, monoclonal target therapy, and radiotherapy. All treatment shows good response to testicular lymphoma.

Declarations

Ethics approval and consent to participate: Yes, please tract the Institutional Review Board with the certificated number of IRB2020104 (Approved on 2021.01.05)

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References

1. Vitolo U, Ferreri AJ, Zucca E. Primary testicular lymphoma. Crit Rev Oncol Hematol. 2008; 65: 183-189.

2. Lagrange JL, Ramaioli A, Theodore CH, Terrier-Lacombe MJ, Beckendorf V, Biron P, et al. Non-Hodgkin's lymphoma of the testis: A retrospective study of 84 patients treated in the French anticancer centres. Ann Oncol. 2001; 12: 1313–9.

3. Vural F, Cagirgan S, Saydam G, Hekimgil M, Soyer NA, Tombuloglu M. Primary testicular

lymphoma. J Natl Med Assoc. 2007; 99: 1277–82.

4. Ornstein DL, Bifulco CB, Braddock DT, Howe JG. Histopathologic and molecular aspects of CD56 + natural killer/T-cell lymphoma of the testis. Int J Surg Pathol. 2008; 16: 291–300.

5. Kim YB, Chang SK, Yang WI, Hahn JS, Koom WS, Shim SJ, et al. Primary NK/T cell lymphoma of

the testis. A case report and review of the literature. Acta Haematol. 2003; 109: 95–100.

6. Park BB, Kim JG, Sohn SK, Kang HJ, Lee SS, Eom HS, et al. Consideration of aggressive therapeutic strategies for primary testicular lymphoma. Am J Hematol. 2007; 82: 840–5.

7. Autorino R, Lamendola MG, De Sio M, Di Trolio RA, Ferraraccio F, Di Lorenzo G. A complete response with rituximab in metastatic diffuse large B-cell lymphoma of the testis: case report.

Int J Immunopathol Pharmacol. 2007; 20: 401–3.

8. 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.

9. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993; 329: 987–94.

10. Kim I, Young RH, Scully RE. Leydig cell tumors of the testis. A clinicopathological analysis of 40

cases and review of the literature. Am J Surg Pathol. 1985; 9: 177-92.

11. Dilworth JP, Farrow GM, Oesterling JE. Non-germ cell tumors of testis. Urology. 1991; 37: 399-417.

12. Al-Agha OM, Axiotis CA. An in-depth look at Leydig cell tumor of the testis. Arch Pathol Lab Med. 2007; 131: 311-7.

13. Kapoor M, Budh DP. Sex Cord Stromal Testicular Tumor. 2021 Mar 25. In: StatPearls [Internet].

Treasure Island (FL): StatPearls Publishing; 2021.

14. 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.

15. Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. Blood. 2014; 123: 486-93.

16. Davies K, Barth M, Armenian S, Audino AN, Barnette P, Cuglievan B, et al. Pediatric Aggressive Mature B-Cell Lymphomas, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020; 18: 1105-1123.

17. Wang Q, Zheng D, Chai D, Wu S, Wang X, Chen S, Wu L, Cao R, Tao Y. Primary testicular diffuse

large B-cell lymphoma: Case series. Medicine (Baltimore). 2020; 99.

18. Chen B, Cao DH, Lai L, Guo JB, Chen ZY, Huang Y, Qiu S, Lin TH, Gou Y, Ma N, Yang L, Liu LR, Wei Q. Adult primary testicular lymphoma: clinical features and survival in a series of patients treated at a high-volume institution in China. BMC Cancer. 2020; 20: 220.

19. Ratkal V, Chawla A, Mishra DK, Monappa V. Testicular non-Hodgkin's lymphoma presenting in a young adult. BMJ Case Rep. 2015 Mar 20; 201.

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