



# 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 tumors are reported to have 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 [6-8]. 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 Dimension 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, even 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 II1 of disease was described as regional lymph nodes involved. Stage II2 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).

## Result

### 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  $68.9 \pm 8.3$  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  $7.8 \pm 10.2$  months (Range 0-30.5 months). The average progression free follow-up duration was  $3.5 \pm 8.7$  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. 7 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  $2.1 \pm 1.2$  (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.

## 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 tumors can be divided into seminoma and non-seminoma. Seminoma includes seminoma and spermatocytic seminoma. On the other hand, non-seminoma includes embryonal carcinoma, endodermal sinus tumor (or known as yolk sac tumor), choriocarcinoma, teratoma, polyembryoma, gonad blastoma [10,12]. Non-germ cell tumor includes sex cord-stromal tumor (Mainly Leydig cell tumor and Sertoli cell tumor), Mixed tumor (Gonad blastoma), Miscellaneous tumors, Hematolymphoid 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 ( $\beta$ -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 our 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 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, 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 cyto-reduction 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. Cyto-reductive 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 misdiagnosed as chronic orchitis or epididymitis [1-3,19]. 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 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. The 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 contains chemotherapy, monoclonal target therapy, and radiotherapy. All treatment shows good response to testicular lymphoma.

## Declaration

### Ethics approval and consent to participate

Yes, please tract the Institutional Review Board with the certificated number of IRB2020104 (Approved on 2021.01.05)

### Consent for publication

Yes, please tract the Institutional Review Board with the certificated number of IRB2020104 (Approved on 2021.01.05)

## Authors Contributions

Dr. Pin-Jui Huang, Dr. Chen-Huang Shen, Dr. Chi-Feng Hung, Dr. Yeong-Chin Jou, Dr. Chang-Te Lin, Dr. Ming-Chin Cheng, and RN. Chin-Hsiung Kang conceived and planned the research. Dr. Pin-Jui

Huang, Dr. Chen-Huang Shen, Dr. Chi-Feng Hung, and Dr. Yeong-Chin Jou carried out the research model. Dr. Yeong-Chin Jou, Dr. Chang-Te Lin, Dr. Ming-Chin Cheng, and RN. Chin-Hsiung Kang planned and carried out the statistical model. Dr. Pin-Jui Huang, Dr. Chen-Huang Shen, Dr. Chi-Feng Hung, and Dr. Yeong-Chin Jou contributed to the interpretation of the results. Dr. Pin-Jui Huang, Dr. Chen-Huang Shen, and Dr. Chi-Feng Hung took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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### Conflict of Interest

No conflict of interest.

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