Primary testicular non-Hodgkin lymphoma. A 10-year Tunisian single-institute experience

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Lymphome non hodgkinien primitif du testicule. Une expérience monocentrique de 10 ans.

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R É S U M É

Prérequis : Le lymphome non hodgkinien primitif du testicule est une localisation extra-ganglionnaire rare, représentant 1 % de tous les lymphomes non hodgkiniens et 1 à 9 % de tous les cancers testiculaires. L'âge median au moment du diagnostic est de 60 ans. La chimiothérapie à base d'anthracyclines est largement utilisée.
But : Analyser les particularités cliniques et les modalités thérapeutiques et évolutives de 6 cas de lymphome non hodgkinien primitif du testicule.
Méthodes : Quarante six cas de cancer testiculaire ont été enregistrés de Janvier 1999 à Janvier 2009. Six cas de lymphome non hodgkinien primitif ont été répertoriés. Nous avons étudié les caractéristiques cliniques et les particularités thérapeutiques et pronostiques de ces 6 tumeurs.
Résultats : L'âge médian de nos patients était de 50 ans et la durée médiane des symptômes était de 4 mois. Tous les patients ont présenté une grosse bourse. Quatre patients avaient des adénopathies abdominals. Le principal sous-type histologique était le lymphome diffus à grandes cellules B. Tous les patients ont eu une orchidectomie par voie inguinale haute. Cinq patients ont eu une chimiothérapie à base d'anthracyclines. Quatre patients ont terminé la chimiothérapie et l'un d'eux a présenté une récidive au bout de 2 ans.
Conclusion : Le lymphome non hodgkinien primitif du testicule est une entité rare. Le pronostic pourrait être aussi bon que dans les formes ganglionnaires grâce aux différents traitements combinés.

M o t s - c l é s
Extra-ganglionnaire; lymphome non hodgkinien; testicule

S U M M A R Y

Background: Primary testicular non-Hodgkin lymphoma (NHL) is an uncommon extra nodal presentation, accounting for 1% of all NHL and 1 to 9% of testicular neoplasms. Median age at time of presentation is 60 years old. Anthracycline based chemotherapies are most frequently used.
Aim: To analyze baseline characteristics, treatment modalities and survival of six cases of primary testicular non-Hodgkin lymphoma.
Methods: We screened 46 testicular neoplasm cases registered from January 1999 to January 2009 and found six primary testicular lymphoma patients. These six cases were analyzed for baseline clinical features, investigations, treatment and outcome variables.
Results: Median age was 50 years old and median duration of symptoms was 4 months. All patients had testicular swelling. Four patients had abdominal lymphadenopathy. Most patients had diffuse large B-cell histology. All patients underwent high inguinal orchidectomy and five were treated with anthracycline based chemotherapy. Four patients completed therapy and one of them relapsed two years later.
Conclusion: Primary testicular NHL is an uncommon entity and with current combined modality treatment, the outcome may be as good as nodal NHL.

K e y - w o r d s
Extranodal; non hodgkin lymphoma; testicular

Non-Hodgkin lymphoma (NHL) of the testis is an uncommon extranodal presentation with incidence rate of 0.06 to 0.09 per 100,000 persons and accounts for about 1% of all NHL [1-4]. It's the most common testicular malignancy in men after 60 years old [1-6]. The diagnosis is usually obtained after orchidectomy, and the dominant histological subtype is diffuse large B-cell lymphoma (DLBCL) [1, 4, 5, 7-12]. Primary testicular lymphoma shows a tendency to spread to several extranodal sites at presentation or relapse, including the contralateral testis, central nervous system (CNS), skin, lung, pleura, Waldeyer's ring and soft tissues [8,9,13,14].

Historically, prognosis was considered to be poor after surgery alone or surgery combined with postoperative radiotherapy [1, 2]. Recently, combined modality treatment with systemic anthracycline based chemotherapy, prophylactic intrathecal chemotherapy and scrotal radiotherapy has been recommended because of the relapse risk to extranodal sites such as the CNS and contralateral testis [1, 7, 8, 12]. Despite these more aggressive treatment modalities, prognosis is often poor, even in the localized disease, with two-year relapse rate exceeding 50% [8, 9, 11, 13, 14].

In this retrospective study, we analyzed baseline characteristics, treatment modalities and survival of six cases of primary testicular non-Hodgkin lymphoma seen at our center from January 1999 to January 2009

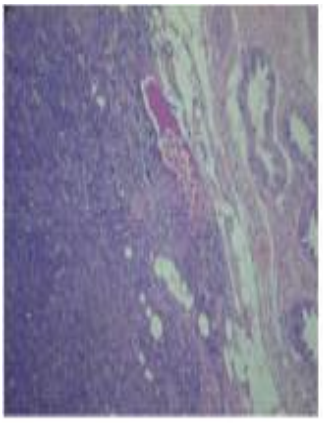
PATIENTS AND METHODS

We evaluated clinical features, management, outcome and survival of 6 adult male patients with primary testicular lymphoma, between 1999 and 2009. Forty-six testicular malignancies were registered and screened in the same period. 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 in patients in complete remission.

RESULTS

Median age was 50 years-old. The left testis was involved in three cases and the right testis in three cases. None of the patients had bilateral testicular involvement. Median duration of symptoms was 4 months. All patients presented with testicular swelling and mild testicular pain. Two patients had general symptoms (one patient suffered from fever and weight loss, the second patient had weight loss). Abdominal CT scan performed in all patients, showed abdominal lymphadenopathy in four patients. Bone marrow involvement was seen in one patient. None had CNS involvement. Three patients presented with high serum LDH levels. Alpha-fetoprotein and HCG were normal in all cases. All patients had B-cell type lymphoma. Five patients had DLBCL histology (Figure 1) and one patient had lymphoblastic B-cell lymphoma. The aim of the treatment was to associate systemic chemotherapy with local treatment. All patients underwent high inguinal orchidectomy as local treatment. None of them received radiotherapy. One patient died 2 months after orchidectomy. Five patients received anthracycline-based chemotherapy, with a CHOP protocol in all cases. Four of whom completed the systemic treatment and one patient died while on treatment. None of the six patients received CNS prophylaxis by intra thecal chemotherapy. Median follow up was 42 months (range 12-78 months). Among the five patients who received chemotherapy, one patient died of neutropenic sepsis during the treatment and four patients responded completely after four to six cycles of chemotherapy. These four patients are now on regular follow up and only one of them relapsed two years after the last treatment in the form of retroperitoneal lymph nodes.

Figure 1: Diffuse large B-cell lymphoma (DLBCL) of the testis



DISCUSSION

Primary testicular lymphoma occurs predominantly in men older than 60 years and represents, in this age group, the most common primary malignant testicular neoplasm [1, 6, 7, 10, 13, 15]. Overall primary testicular lymphoma accounts for 1 to 9% of testicular neoplasms, 2% of high grade lymphomas and 5% of extra nodal lymphomas in men [1, 6, 7, 10, 13, 15, 16]. Primary testicular lymphoma rarely occurs in pediatric patients, most of whom are prepubertal [17].

Testicular location of the lymphoma is often unilateral. It can be bilateral in 5 to 20% of cases [16, 18, 19]. Bilateral involvement at initial presentation is rare except with lymphoblastic lymphoma [15]. In our series, no patient had bilateral disease. The most common clinical presentation is unilateral and painless testicular swelling [1, 7, 8, 15]. Fever, night sweats and weight loss are rarely encountered and are associated with aggressive forms of lymphoma [12]. These symptoms were seen in two of our patients.

Published series reported the dominance of B-cell type and the major lymphoma subtype is DLBCL [4, 5, 7, 9, 14, 15, 16, 20-22]. In the largest series published [4] which involved 3669 cases of testicular NHL registered from 1985 to 2004, DLBCL accounted for 77.8% of cases. Other B-cell types and T-cell types were seen in 21.1% and 1.1% of cases respectively. In our

series, DLBCL subtype was encountered in five patients and lymphoblastic form in only one patient. Orchidectomy allows the diagnostic of testicular lymphoma and represents its first therapeutic procedure [5, 7]. Even in the localized stages, the only orchidectomy is insufficient. Indeed, more than 60% of patients treated by simple orchidectomy relapsed in the five first years especially in the central nervous system [5, 7]. In our series, one patient died from his disease 2 months after orchidectomy. Therefore, most of the authors propose some form of adjuvant treatment; the choice of this further treatment is still a matter of debate owing to the rare incidence of the disease and the absence of prospective randomized studies.

Systemic doxorubicin-based chemotherapy has been widely used also in patients with localized disease, since early retrospective reports indicated an improved outcome by adding anthracycline-containing chemotherapy to surgery [1, 11, 14, 19-21]. On the other hand, according to Fonseca et al [22] and Seymour et al [23], no benefit was noted; even with adjuvant systemic chemotherapy, a continuous risk of relapse has been observed, especially in CNS and other extranodal sites including the contralateral testis [9, 24]. In our series, five patients had an anthracycline based chemotherapy. One died during the treatment course and one had nodal recurrence 2 years later. CNS relapse is considered to be common, but whether prophylactic CNS directed therapy prevents relapse or not has not been consistently reported [1,14]. Connors et al [3] reported that they encountered no CNS relapses following combined modality treatment and suggested that the chemotherapy, by promptly eradicating systemic micrometastasis, prevents later seeding of CNS. In other series, chemotherapy was not shown to reduce the incidence of CNS relapses [19]. CNS directed therapies have been utilized and have shown promising results in preventing CNS recurrences [23]. However, the role of intrathecal chemotherapy as CNS prophylaxis is controversial and relapses including CNS have been reported even in patients receiving intrathecal chemotherapy [25, 26]. Recurrence in contralateral testis has been reported in approximately 5 to 20% of cases [7, 9, 11]. Scrotal radiotherapy in order to prevent relapse in the contralateral testis seems to be beneficial, especially for patients with localized disease [9, 14, 24]. None of our patients received contralateral scrotal radiotherapy and none developed contralateral testis recurrence up to the last follow up. Because of the spreading nature and relapse probability at different sites, including central nervous system and contralateral testis, systemic treatment with doxorubicin-based chemotherapy associated or not to contralateral testis and CNS prophylaxis seems to improve the outcome of primary testicular lymphoma [20]. Despite these aggressive therapeutic modalities, prognosis is often poor, even in localized forms, with a two-year relapse rate exceeding 50% [9, 11, 13, 14, 20]. The International Extranodal Lymphoma Study Group reported that, of 373 retrospectively evaluated patients with primary testicular lymphoma treated with different modalities, the overall survival rate was 81% and progression free survival was 68% at five years. At a median follow-up of 7.6 years, 195 patients (52% of cases) had relapsed and the most frequent sites of recurrence were CNS and contralateral testis [9].

CONCLUSION

The management of patients with testicular lymphoma presents several challenges. Because of the poor prognosis, an aggressive treatment approach is warranted. However, testicular lymphoma is predominantly a disease of older men who often have limited ability to tolerate aggressive treatment. Considering the rarity of disease, it will be difficult to standardize the therapeutic and preventive strategies through randomized trials. Treatment will continue to evolve with improved understanding of the molecular and genetic characteristics of testicular lymphoma, identification of patients at higher risk of relapse and with incorporation of newer drugs into current regimes of chemotherapy.

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