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Primary Testicular Lymphoma: A Case Report and Review of the Literature

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Abstract

Background and Aim: Primary testicular lymphoma (PTL) is a rare form of extranodal non-Hodgkin's lymphoma. It represents for 1% - 2% of non-Hodgkin's lymphoma, and mostly affects the elderly. We describe an interesting case of PTL managed by a combined multimodal approach with a review of the literature. ***Case Presentation***: Patient aged 56 years, consulted for an increase in the volume of the right testicle without associated pain, all evolving in the context of a slight decline in general condition. Clinical examination revealed a large painless mass in the right scrotal bursa. A scrotal ultrasound showed a right intra-testicular mass. The patient had undergone inguinal orchiectomy. Pathological analysis showed diffuse large B-cell lymphoma of the testis. Whole-body 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET-CT) showed no suspicious hypermetabolism. Lumbar puncture did not reveal malignant cells in the cerebrospinal fluid (CSF). The patient then received 6 cycles of chemotherapy according to the R-CHOP protocol (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) and 2 cycles of intrathecal methotrexate. After chemotherapy, scrotal radiotherapy at a dose of 30 Gy was delivered. The evolution was marked by the death of the patient six months after the end of the scrotal radiotherapy following a diffuse lymph node relapse with a profound alteration of the general state. ***Conclusion***: The treatment depends imperatively on the stage of the disease. The therapeutic approach is multimodal and combined based on orchiecto-

my, systemic and intrathecal treatment and scrotal radiotherapy. PTL is an aggressive malignant with a poor prognosis. Randomized trials are needed to define a better therapeutic strategy.

Keywords

Primary Testicular Lymphoma, Diffuse Large-B Cell Lymphoma, Orchiectomy, Chemotherapy, Radiotherapy, Testis

1. Introduction

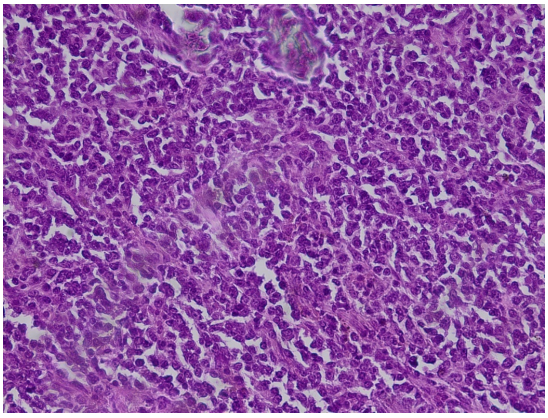
Primary testicular lymphoma (PTL) is a rare form of extranodal non-Hodgkin's lymphoma [1]. Diffuse large B-cell lymphoma is the most predominant histological variety [2]. It is the most frequent testicular malignancy in men over 60 years of age. Its prognosis is usually poor, characterized by spreading to non-contiguous extranodal sites, especially in central nervous system and high recurrence [3] [4] [5].

Few studies are published in our country about PTL. We report a new observation of unilateral localized PTL without specific symptoms in a 56-year-old patient, managed by a combined multimodal approach, with a review of the literature.

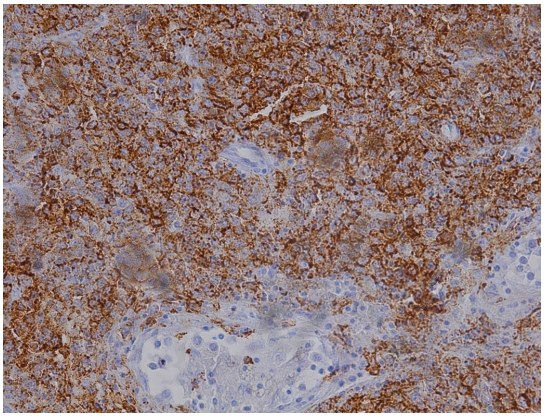
2. Case Report

Mr. I. B, 56 years old, father of 3 children with a family history of breast cancer without associated comorbidities. The onset of his symptomatology was in May 2019 with the observation of an increase in the volume of the right testicle without associated pain, all evolving in the context of a slight decline in general condition. The clinical examination revealed a large painless mass in the right scrotal bursa, the lymph nodes were free. There was no splenomegaly or hepatomegaly. A scrotal ultrasound showed a large, hypoechoic, discretely polylobed, hypervascularized right intra-testicular mass suggestive of a seminoma.

Tumor marker assay showed human chorionic gonadotropin (BHCG) at 0.38 mU/ml and alpha-fetoprotein (AFP) at 1.76 U/ml. The patient had undergone an inguinal orchiectomy. Anatomopathological analysis showed a 5.5 cm undifferentiated malignant tumor of the right testicle with an invasion of the spermatic cord. The immunohistochemical study confirmed the diagnosis of a diffuse large B-cell lymphoma of the testis with a diffuse expression of CD 20 (**Figure 1**) and without expression of CD 3, CD 10, PLAP and c Kit. The tumor was classified as pT3 according to the International Union Against Cancer (UICC) classification. Postoperative scrotal ultrasound showed a free right orchiectomy compartment. Whole-body 18-fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG-PET-CT) did not show any suspicious hypermetabolism. The lumbar puncture did not reveal any malignant cells in the cerebrospinal fluid (CSF). HIV serology was negative. The patient then



(a)



(b)

Figure 1. (a) HE ×400, Microscopy shows large tumor cells with irregular and enlarged nuclei with dense or vesicular chromatin, nucleolated and surrounded by cytoplasm with ill-defined boundaries; (b) CD20 ×400, Dense and diffuse over expression of CD20.

received 6 cycles of chemotherapy according to the R-CHOP protocol (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) with 21-day intervals between the cycles, as well as 2 cycles of intrathecal methotrexate.

After chemotherapy, our patient received scrotal radiotherapy. For this purpose, a dosimetric scan in the treatment position was performed. The patient was in supine position, thighs spread, legs slightly flexed to free the scrotum and the perineal region. Between the spread thighs we had placed a material to support the posterior part of the scrotum and protect the perineum. The penis was lifted and immobilized against the abdomen. The CT images were obtained by thin sections of 2.5 mm and exported to a delineation console.

The entire scrotum was delineated as the clinical target volume (CTV). The planning target volume (PTV) was obtained by applying a 1 cm margin around the CTV. The organs at risk, namely the rectum, bladder, anal canal, penile urethra and penile bulb, were delineated. The treatment planning by a three-dimensional conformal technique was performed with 2 anterior oblique beams with wedge filters. The dose was 30 Gy with 2 Gy per fraction and 5 sessions per week (**Figure 2**). The treatment was well tolerated. The evolution was marked

Figure 2. Three-dimensional 3D conformal radiotherapy using 2 anterior oblique beams with wedge filters.

by the death of the patient six months after the end of the scrotal radiotherapy following a diffuse lymph node relapse with a profound alteration of the general state.

3. Discussion

PTL is a rare pathology that represents 1% - 2% of all malignant non-Hodgkin's lymphomas, 4% of all extranodal malignant non-Hodgkin's lymphomas and 5% - 9% of malignant testicular tumors [3] [4] [6].

PTL concerns mainly men over 50 years of age as shown by most prospective and retrospective studies [3] with a median age of 65 years [4] [7]. The age of our patient was 56.

The usual symptomatology is a progressive increase in testicular volume over several months without pain [3] [4]. It may be accompanied by fever, weight loss, or night sweats [5]. The presence of these systemic signs is predictive of tumor aggressiveness and is observed in 25% to 41% of patients with advanced disease [4] [8]. The symptomatology was similar in our patient but general signs were absent.

The classic physical sign in the localized stage is a solid testicular mass of variable size. This mass can be unilateral or bilateral. Bilateral localization is the most frequent according to the literature [3]. It is synchronous in 10% and asynchronous in 30% - 35% [9]. Our patient had a unilateral lesion.

Complementary examinations help to determine the unilateral or bilateral nature and the extent of the disease. Scrotal ultrasonography is the first-line examination for an enlarged scrotum [4] [10]. It is often coupled with Doppler. It allows the mass to be highlighted with its measurements. It may show circumscribed or diffuse hypoechoic areas and testicular hypervascularization [10].

Lactate dehydrogenase (LDH) levels are elevated, while BHCG and AFP are rarely elevated [11]. BHCG and AFP markers were normal in our patient.

Orchidectomy is essential because it is of diagnostic and therapeutic interest [1] [3] [5] [12]. It is performed through an inguinal approach. It removes the so-called sanctuary site [3] [6]. In the presence of the blood-testicular barrier, the drugs penetrate the testicles with difficulty and the effect of chemotherapy is not ideal [13]. At the same time, testicular tumor cells may also express high levels of drug-resistant proteins, such as P-glycoprotein (PGP) and breast cancer drug-resistant protein (BCRP), resulting in resistance to chemotherapy [14].

The most common histologic subtype is diffuse large B-cell lymphoma, accounting for approximately 80 - 90% of testicular lymphomas [2] [5] [6] [15]. On immunochemistry, tumor cells usually express pan-B-cell markers such as CD19, CD20, CD22, CD79a and PAX5. Surface and cytoplasmic immunoglobulins (Ig), most commonly IgM, are demonstrated in the majority of cases, and the Ki-67 proliferation index is high [15]. T-cell and Burkitt's lymphomas have also been described [2].

In recent years, numerous studies have been conducted on tumor biology in-

cluding the tumor microenvironment (TME) and tumor-related immunity. The roles of the NF-κB signaling pathway, 9p24.1 aberrations, and tumor-infiltrating immune cells, and in particular the expressed immune checkpoints, appear to be unique compared to other lymphomatous entities [16].

Lumbar puncture for tumor cells in the CSF is recommended because the central nervous system is a preferred metastatic site [1]. Brain MRI is recommended in some studies [5] [17]. Other metastatic sites include skin, lung, contralateral testis, Waldeyer's ring [5] [6].

For a long time, bone marrow biopsy and thoracic-abdominal-pelvic CT scans were used to differentiate between localized and metastatic disease [5]. Whole-body 18-fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG-PET-CT) has a prominent place in the initial workup of lymphoma. It is more sensitive for the detection of other extra-ganglionic lesions [16] [17].

The Ann-Arbor classification is the staging system for primary testicular lymphomas. The vast majority (70% - 80%) are diagnosed at a localized stage (stage I - II) [6] [7] [9]. Advanced stages (stage III - IV) are very rare [1] [15].

Due to the low incidence of the disease, no randomized phase III trials have been conducted and the therapeutic approach is based on data from phase II trials and retrospective studies [16]. A multimodal therapeutic approach is needed. The multidisciplinary team includes urologists, hematologists and radiation oncologists [18].

R-CHOP chemotherapy followed by central nervous system chemoprophylaxis and scrotal radiotherapy is the standard treatment for localized stage I - II PTL [6] [19] [20].

Although there are conflicting data on the best strategy to reduce CNS recurrence, two options can be considered. Intrathecal chemotherapy with methotrexate (MTX) is the most commonly used and systemic intravenous MTX is an alternative [21].

The incidence of central nervous system involvement varies between studies and can be as high as 44% [22]. The combination of rituximab with anthracycline-based chemotherapy has not impacted CNS relapse rates [1] but has been shown to impact progression-free survival as well as overall survival for diffuse large B-cell lymphoma [2] [7] [20]. Methotrexate has been used intrathecally for CNS prophylaxis in numerous studies [1].

Patients treated with orchiectomy followed by chemotherapy without scrotal radiotherapy have a significant risk of relapse, especially in the contralateral testis, estimated at 25% [1] [23]. Indeed, chemotherapy drugs have a low penetration in the healthy testis [3]. However, the results of numerous studies attest that scrotal irradiation is associated with a better survival [2] [3] [6].

Prophylactic scrotal radiation therapy at a dose of 30 Gy is a significant factor in improving overall survival [1] [2] [3].

Prophylactic scrotal irradiation in the retrospective International Extranodal Lymphoma Study Group (IELSG) was associated with a reduction in the inci-

dence of testicular relapse from 35% to 10% [3]. This benefit of local control was associated with an improvement in both progression-free survival and 5-year overall survival [2] [3] [5].

The anatomic target volume (ATV) should contain the testis, epididymis, spermatic cord and albuginea [3] [5]. The skin is not systematically included in the CTV except in case of scrotal skin invasion. A margin of 1 cm around the CTV is applied to obtain the projected target volume [3] [5]. Considering the mobility of the testis in the scrotum and the histopathological findings, adjuvant irradiation of the entire scrotum, including the contralateral testis, is recommended [3].

For optimization of the treatment and protection of organs at risk (OAR) the dosimetric scan can be done with the patient in supine position with legs widely spread. An attenuation material at the posterior part of the scrotum can be put on to reduce the dose to the anus [3]. The scrotal skin dose reduction may result in a dose reduction to the tunica albuginea adjacent to the skin. Charlotte et al noted invasion of the tunica albuginea in 40% of cases and suggest no reduction of the treatment dose to the scrotal skin [3] [24].

According to the data of the retrospective analysis conducted by the IELSG, doses lower than 30 Gy would be associated with a lower survival rate, therefore the dose of 30 Gy can be considered as a standard in prophylactic scrotal irradiation with a classical fractionation [3].

Side effects are expected by impairment of endocrine (hypogonadism) and exocrine function of the testis (infertility) with a dose of 30 Gy [3].

Several radiotherapy techniques have been described for scrotal irradiation. Modern techniques using high energy electrons 25 MeV and/or Megavolt photons 4 - 8 MV currently allow more adequate coverage of the planned treatment volume than the old techniques using low energy electrons (4 - 8 MeV) [3]. Treatment planning with 2 oblique beams with wedge filters has shown the best PTV coverage with minimal dose to the surrounding organs [3]. Our patient benefited from this technique.

In advanced stages (III - IV), the standard treatment remains chemotherapy with anthracyclines associated with Rituximab. Intrathecal chemotherapy is recommended regardless of the stage of the disease to prevent CNS relapse. The role of scrotal radiotherapy is controversial in these stages [6] [8] [24].

The prognosis of primary testicular lymphoma is poor with historically a 5-year overall survival rate of 17% - 48% and is negatively related to advanced stage, advanced age, B-symptoms, and high International Prognostic Index (IPI) score [1] [25]. An elevated LDH level has also been correlated with tumor aggressiveness [1] [11].

The use of multimodal therapy is associated with an increase in the 5-year survival rate from 30% to 86.6% [1] [7]. Relapses are often frequent, particularly in the CNS, despite a well-conducted therapeutic protocol according to international standards [1] [16].

The emergence of targeted therapies and checkpoint inhibitors has considerably modified cancer treatments. Ongoing phase II studies and future clinical trials will determine the role of PD 1 - PDL1 blockade, and the growing understanding of MCT would bring, more therapeutic options [16].

4. Conclusion

PTL is a rare and aggressive extranodal non-Hodgkin's lymphoma. Despite its low incidence, it is the most common testicular cancer in the elderly. It is characterized by extension to non-contiguous extranodal sites, particularly in the CNS, a high recurrence rate and a poor prognosis. Its management is complicated and requires a multidisciplinary approach. Randomized clinical trials are needed to define better therapeutic strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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