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Case report

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A case of primary testicular and epididymal non-Hodgkin's lymphoma in a geriatric patient

Abstract

Introduction: Primary extranodal non-Hodgkin's lymphoma of the testicle and epididymis is a rare entity with poor prognosis, high relapse rates, and a strong tendency for central nervous system dissemination. It predominantly affects men over 60 years old, with diffuse large B-cell lymphoma being the most frequent subtype.

Aim: To describe the clinical and therapeutic management of a frail elderly patient with primary extranodal non-Hodgkin's lymphoma of the testicle and epididymis, emphasizing the feasibility and tolerability of trimodal treatment even in the context of clinical frailty and multiple comorbidities.

Report of case: A 78-year-old man with multiple comorbidities presented with a long-standing, painless right testicular mass. Ultrasound showed heterogeneous nodules and hydrocele. Radical orchiectomy confirmed diffuse large B-cell lymphoma involving both the testicle and epididymis. The case was staged as clinical IE, intermediate risk according to National Comprehensive Cancer Network International Prognostic Index, with no nodal or distant involvement. The patient received six cycles of chemotherapy and adjuvant scrotal radiotherapy (30Gy in 15 fractions) delivered using a three-dimensional conformal electron beam technique, ensuring optimal target coverage and reduced toxicity to surrounding organs. Intrathecal prophylaxis was omitted due to clinical frailty. At 10 months follow-up, the patient remains in remission without significant late toxicity.

Conclusion: Combined therapy including surgery, chemotherapy, and radiotherapy is associated with improved overall and progression-free survival in primary extranodal non-Hodgkin's lymphoma of the testicle. Electron beam radiotherapy provides favorable dosimetry and reduced toxicity. Despite frailty, this patient tolerated full trimodal therapy with a favorable response. Trimodal treatment with omission of intrathecal prophylaxis proved safe and effective in this frail elderly patient, achieving disease control while maintaining quality of life.

Keywords: non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, frail elderly, orchiectomy, chemotherapy, radiotherapy, toxicity

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Abbreviations: ENHL, extranodal non-Hodgkin's lymphoma; NCCN-IPI, national comprehensive cancer network international prognostic index; R-CHOP, rituximab, cyclophosphamide, doxorubicin and vincristine; ECOG, eastern cooperative oncology group; 3DCRT, three-dimensional conformal radiation therapy; DLBCL, indicating diffuse large B-cell lymphoma; non-GCB, non–germinal center; ABC, activated B-cell; BTK, bruton's tyrosine kinase; IPI, international prognostic index; CNS, central nervous system; IFRT, involved-field radiotherapy.

Introduction

Extranodal Non-Hodgkin's Lymphoma (ENHL) is a rare form with a poor prognosis, accounting for up to 35% of primary lymphomas at diagnosis. Its primary manifestation in the testicle and epididymis is particularly uncommon (1-2% of NHL cases), featuring a distinct clinical profile characterized by central nervous system (CNS) tropism, high recurrence rates, and a predilection for men aged 60 years or older.[1,2]

Consequently, therapeutic advances have been slower and less certain, making international collaborative efforts through registries and studies crucial to generate knowledge that can optimize outcomes. This is especially relevant when focusing on frail elderly patients, as discussed in this article.

Case report

A 78-year-old elderly man, with no personal or family history of cancer, former smoker and alcohol user, presented with chronic non-communicable clinical comorbidities, most notably cerebral vascular disease and dementia. He reported a progressively enlarging, painless right testicular swelling for one year, with no associated symptoms On examination, there was no lymphadenopathy, splenomegaly or hepatomegaly. Scrotal ultrasound revealed an enlargement right testicle with heterogeneous nodules up to 1 cm in diameter and a marked right hydrocele.

Serum levels of human chorionic gonadotropin, alpha-fetoprotein, blood count índices, and lactate dehydrogenase were within normal limits. However, the erythrocyte sedimentation rate (48 mm/h) and beta-2 microglobulin (3.391 mg/L) were elevated.

He underwent right radical orchiectomy. The pathological examination revealed a well-defined nodular tumor, encapsulated by a smooth whitish capsule, measuring 1.5 × 9.8 × 0.1 cm. Microscopy demonstrated a diffuse proliferation of large B-lymphoid cells involving both the testicle and epididymis. Immunohistochemical analysis confirmed the diagnosis of diffuse large B-cell non-Hodgkin's lymphoma (Table 1).

Table 1 Immunohistochemistry results of right radical orchiectomy

Marker	Clone	Expression
BCL-2	124	Positive
BCL-6	PG-B6P	Negative
CD10	56C6	Negative
CD138	MI15	Negative
CD20	L26	Positive
CD23	CD23	Negative
CD3	Rabbit polyclonal	Negative
CD5	4C7	Negative
Cyclin D1	EP12	Negative
c-MYC	EP121	Positive (80% of cells)
Ki-67	MIB-1	Positive (95% of cells)
MUM1	MUM1P	Positive
TdT	EP266	Negative

Bone marrow biopsy, cerebrospinal fluid analysis, serology, and staging studies showed no nodal or distant disease and no evidence of infection, confirming clinical stage IE according to the Ann Arbor classification.

Based on the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), the patient was categorized as low-intermediate risk.

Adjuvant chemotherapy was administered according to the R-CHOP protocol based on rituximab, cyclophosphamide, doxorubicin and vincristine, every 21 days for six cycles, without interruption or acute toxicity.

Intrathecal prophylaxis with methotrexate was omitted after weighing risks and benefits, due to advanced age, low muscle mass, preexisting cognitive decline, multiple comorbidities, frailty, borderline performance status (Eastern Cooperative Oncology Group – ECOG 3), and controversial evidence in the literature.

Radiotherapy followed. The patient was positioned supine with the penis lifted and fixed to the abdomen. During delineation and treatment planning, organs at risk (rectum, anal canal, bladder, and femoral heads) were carefully contoured and spared. Treatment was delivered using a three-dimensional conformal radiation therapy (3DCRT) technique at a dose of 30 Gy in 15 fractions (2 Gy/day, five times per week). Radiotherapy was completed without complications, with good tolerance and no treatment interruptions. The only acute toxicity observed was self-limited grade II radiodermatitis.

At 10 months after completion of therapy, the patient remains in oncology follow-up, with no signs of disease recurrence and no evidence of significant clinical signs regarding late toxicity to the local treatment.

Discussion

Primary ENHL of the testicle and epididymis is a rare neoplasm, making robust epidemiological studies and randomized clinical trials difficult to conduct. Despite its low incidence, it represents the most common testicular malignancy in elderly men.[2] The clinical presentation, as seen in this case, is typically insidious, limited to local symptoms such as testicular swelling, and often with a prolonged evolution lasting months — approximately one year in the present report. The absence of constitutional ("B") symptoms, a factor associated with a better prognosis, is consistent with classical descriptions of the disease.[1–5]

From a histopathological point of view, the present case corroborates the literature, which points to Diffuse Large B-Cell Lymphoma (DLBCL) as the predominant subtype, responsible for 88% to 98% of cases.[2,3,4,6]

Histopathologically, this case supports the literature indicating diffuse large B-cell lymphoma (DLBCL) as the predominant subtype, responsible for 88–98% of cases. [2,3,4,6] Immunohistochemical analysis suggested a non–germinal center (non-GCB) molecular subtype, probably of the activated B-cell (ABC) type, characterized by MUM1 positivity and CD10/BCL-6 negativity. This finding is clinically relevant since the ABC subtype is linked to specific molecular alterations and a potentially less favorable prognosis, though it also opens the possibility for benefit from targeted therapies such as Bruton's tyrosine kinase (BTK) inhibitors.[7]

Although rare, other histological variants have been reported, including mantle cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma, and Burkitt lymphoma.[6,3]

Advanced age is among the most consolidated prognostic factors in testicular ENHL. The patient in this study, aged over 75, falls precisely within the group associated with the poorest prognosis. This correlation can be explained by the fact that diagnosis at older ages is associated with molecular and genetic alterations accumulated over time – such as the ABC subtype, MYC or BCL-2 expression, and BCL-6 locus abnormalities – all of which negatively impact outcomes. Compounding these intrinsic disease factors are age-related physiological changes, including overall clinical decline, reduced body mass reserve, diminished function of vital organs involved in drug metabolism, and a higher prevalence of comorbidities. Consequently, older patients often exhibit lower tolerance to anticancer therapy, which frequently limits dose intensity and treatment adherence.[2,5,8,9]

The impact of age is quantified by prognostic indices. The original International Prognostic Index (IPI) used a binary age cutoff of 60 years. Subsequent refinements led to the NCCN-IPI, which introduced a three-tiered age stratification, assigning up to three points for advanced age.[2,5,8,9] Based on the NCCN-IPI criteria, the patient was classified as intermediate-risk, a stratification in which his advanced age was a determining factor. His age of over 75 years significantly contributed to the final score, reflecting its substantial negative impact. This intermediate-risk classification underscores the considerable weight of age in prognostic assessment, potentially reclassifying a patient profile that might otherwise be considered lower risk. It is important to emphasize that, aside from advanced age, other poor prognostic factors described in the literature were not present in this case.

The curative treatment for localized ENHL of the testicle is trimodal therapy, comprising radical orchiectomy followed by adjuvant chemoradiotherapy. The best overall and progression-free survival outcomes are achieved with this combined approach, with five-year survival rate up to 87%. Worse outcomes are consistently observed, regardless of clinical stage, in patients who do not receive the full combined regimen. However, the low prevalence of robust studies—particularly in the era of modern therapies like immunotherapy, targeted agents, and checkpoint inhibitors—hinders a deeper understanding of outcomes for patients with primary testicular and epididymal ENHL treated with trimodality. [2,4] A crucial particularity in managing this disease is the high risk of relapse in immunoprivileged sites ("sanctuaries"), such as the central nervous system (CNS) and the eyes. [2-5] To mitigate this risk, CNS prophylaxis with methotrexate (intrathecal or intravenous) is an integral componente of the trimodal strategy. The IELSG10 and IELSG5 studies demonstrated that this approach, based on the R-CHOP protocol combined with CNS prophylaxis, reduces the incidence of

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CNS recurrence to rates between 6% and 13% at 5 years for patients with localized disease. The feasibility of administering intravenous methotrexate after R-CHOP was later corroborated by IELSG30, a phase 2 study.[10]

However, the decision to administer CNS prophylaxis is not without controversy, as the practice lacks support from randomized clinical trials. Furthermore, it's potential neurotoxic effect must be considered. Chemotherapy-induced leukoencephalopathy, also described as "chemobrain" or chemotherapy-associated cognitive impairment, is a significant adverse effect, particularly in high-dose regimens. Therefore, the decision to implement prophylaxis should involve a thorough analysis, weighing the benefit of protecting an immunoprivileged site against the risk of inducing iatrogenic damage, while also considering the patient's pre-existing neurological comorbidities. [11-13] In the present case, CNS prophylaxis (either intrathecal or intravenous) was not administered. Although the patient experienced no CNS recurrence during follow-up, it is essential to emphasize that therapeutic failure in the CNS, particularly for lymphomas of extranodal sites, can occur late (≥6 years), requiring prolonged vigilance.[10]

Adjuvant radiotherapy is a fundamental pillar for local disease control and relapse prevention, particularly in the contralateral testicle, where it can reduce the risk of recurrence by up to 25%. This protective effect is necessary due to the reduced efficacy of chemotherapy in this site. [2,5] Radiotherapy is a well-established tool in oncological treatment, grounded in the principles of radiobiology. The high radiosensitivity of lymphocytes, first demonstrated in cell cultures by Kwan and Norman in 1977, is attributed to these cells' intrinsic characteristics. Key factors include their low capacity for DNA repair, which renders them vulnerable to direct or indirect damage (mediated by reactive oxygen species); high rates of proliferation and differentiation; and a quiescent (resting) state. These characteristics culminate in a propensity for cell death through various mechanisms, including apoptosis (type I), autophagy (type II), and/or regulated necrosis (type III).[14,15]

In this case, adjuvant scrotal radiotherapy was delivered at the standard dose of 30 Gy in conventional fractionation, which is associated with improved survival outcomes. Treatment was delivered using oblique electron fields (6 MeV) to ensure coverage of the target volume while minimizing dose to organs at risk, optimizing tolerance, and maintaining adherence. For more advanced stages (Ann Arbor IIE), involved-field radiotherapy (IFRT) is recommended, as demonstrated in the IELSG-1 study. In this approach, the radiation field includes only the macroscopically involved tissue plus a safety margin. The IFRT technique can vary from minimal modality (restricted to limited involvement of para-aortic lymph nodes) to maximal ("inverted Y" field, including the para-aortic and bilateral pelvic regions). The recommended prophylactic dose is 30 Gy (range 24-40 Gy) for the testicular region; 30–35 Gy to the lymph nodes for patient with a complete response to chemotherapy; and 35–45 Gy for those with a partial response.[16]

This case demonstrates the management of a very elderly, neurologically impaired, and frail patient with newly diagnosed primary testicular and epididymal ENHL — a clinical scenario typically associated with poor prognosis. Despite the omission of intrathecal prophylaxis, the patient tolerated full trimodal therapy well, with manageable toxicity and meaningful disease control to date. However, long-term recurrence cannot yet be assessed due to limited follow-up duration.

Conclusion

Combined therapy including surgery, chemotherapy, and radiotherapy is associated with improved overall and progression-free survival in primary extranodal non-Hodgkin's lymphoma of the testicle. Electron beam radiotherapy provides favorable dosimetry and reduced toxicity. Despite frailty, this patient tolerated full trimodal therapy with an excellent clinical response.

The trimodal approach, with omission of intrathecal prophylaxis, proved to be safe and effective in this frail elderly patient. It minimized the risk of chemotherapy-induced cognitive impairment while achieving durable disease control and preserving quality of life.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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