Abnormal presentation of a bilateral, synchronous and plurimetastatic medium and large cell testicular lymphoma: A case report

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Abstract. Primary testicular lymphoma (PTL) accounts for 1-2% of all cases of non-Hodgkin's lymphoma, with a higher incidence in patients aged >60 years. The most common histological subtype is diffuse large-cell B lymphoma. By contrast, the bilateral synchronous and multimetastatic clinical presentation is a rare and unusual clinical presentation. In testicular masses, orchiectomy is essential for histopathological evaluation of the disease and definition of the immunophenotypic structure. The present study reported the case of a paucisymptomatic 54-year-old patient, who presented with erectile dysfunction and increasing testicular volume. Although clinical assessment and ultrasound examination showed an abnormal structure, highly suspicious for testicular cancer, the subsequent bilateral radical orchiectomy permitted the diagnosis of an unusual and rare PTL with multiple metastases reported at the PET/CT scan. In conclusion, the rare and aggressive disease represented by PTL requires a multidisciplinary approach and an aggressive treatment in order to provide the best care for patients affected.

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Abbreviations: PTL, primary testicular lymphoma; NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; IIEF, International Index of Erectile Function; US, ultrasound scan; WBC, white blood cells; RBC, red blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; hCG, human chorionic gonadotropin; 18F-FDG, fluorodeoxyglucose; PET/CT, positron emission tomography-computed tomography; SUV, standardized uptake value; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; PFS, progression free survival; OS, overall survival; CNS, central nervous system

Key words: lymphoma, testicular cancer, bilateral, metastatic, case report

Introduction

Primary testicular lymphoma (PTL) is an uncommon and aggressive form of extra-nodal non-Hodgkin's lymphoma (NHL), accounting for 1-2% of all NHL cases in patients aged >60 years (1). The most common histological subtype is the diffuse large B-cell lymphoma (DLBCL), which is characterized by a high aggressiveness, rapid growing mass and extranodal tropism, comprising a bilateral involvement in 6-10% of cases (2). Typical clinical manifestations include the presence of a firm and painless testicular mass, although orchitis-like symptoms could be present. In addition, despite non-disease-specific, hydrocele is observed in 43% of patients with primary and secondary testicular lymphoma (1,3). Despite PTL involves testes only at the beginning of the disease, the involvement of other sites at the time of diagnosis is common, in particular central nervous system (CNS) skin, lung and pleura (4). On echotomography, PTL is indistinguishable from other neoplastic and non-neoplastic lesions (5). As result, diagnosis is obtained via histological confirmation post-orchiectomy, which permits the staging of the disease and the subsequent therapy choice (6).

Case report

A 54-year-old patient presented to our attention at the Hospital 'Sacro Cuore di Gesù' Fatebenefratelli (Benevento, Italy) in October 2021, complaining severe erectile dysfunction (International Index of Erectile Function questionnaire score <7) in addition to a bilateral and rapid increase in volume and consistency of testes, in absence of painful manifestations. Other non-urological symptoms included

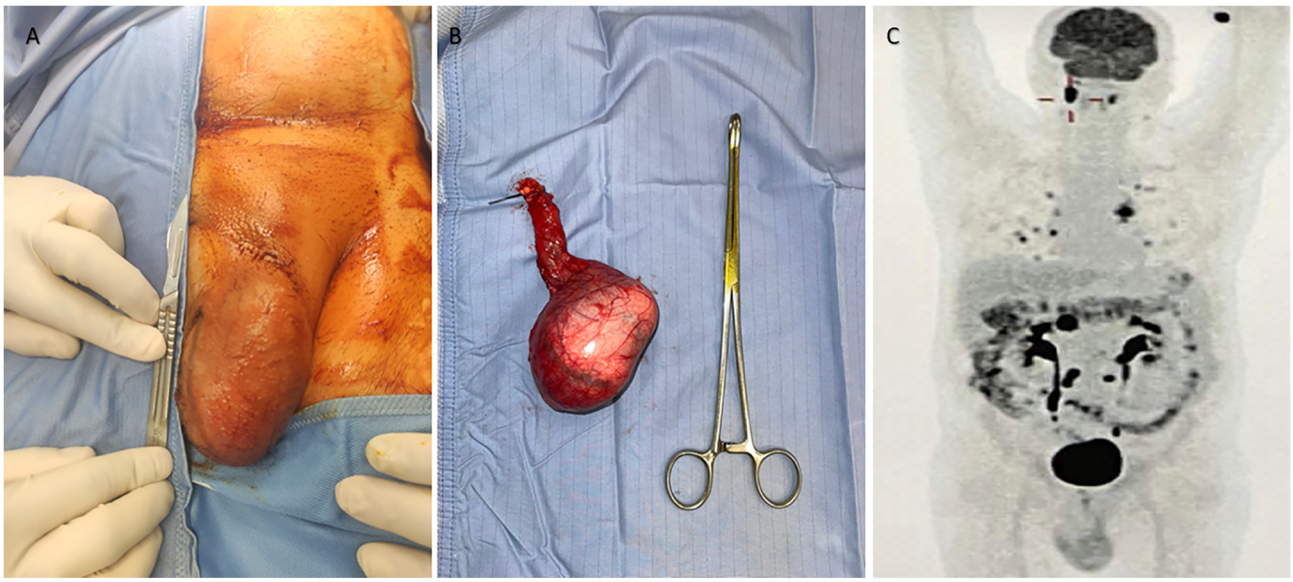

Figure 1. (A) Testes before surgery. (B) Testes removed. (C) PET/CT scan after surgery. PET/CT, positron emission tomography-computed tomography.

gingivitis, mastoiditis, headache and dysgeusia. No recent traumatic or septic issues were reported in the anamnesis. Among comorbidities, patient suffered from hypertension and gastroesophageal reflux disease (GERD), which however was in treatment with amlodipine 10 mg and Omeprazole 40 mg per day. The patient was negative for Hepatitis B and C Viruses (HBV and HCV) as well as Human Immunodeficiency Virus (HIV). Physical examination excluded hydrocele, showing a significant increase of both testis volume, with a wooden consistency and immobility compared to the scrotal plane. Ultrasound scan (US) examination confirmed the increased size of testes, revealing a completely subverted structure due to the presence of coarse and confluent hypo-echogenic areas, enhancing at the colour-Doppler modality. Blood samples were obtained, reporting a mild hypotestosteronaemia (179 ng/dl, normal values 350-890 ng/dl) and increased LDH (348 IU/l, normal values 80-300 IU/l), while alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and human chorionic gonadotropin (hCG) were within normal ranges (4.13 ng/ml, 4.34 ng/ml and 2.1 mIU/ml, respectively; normal values: <6 ng/ml, <5 ng/ml and <5 mIU/ml, respectively). Regarding blood count, renal and liver function, the patient reported no pathologic values with $8.16x10^3/\mu l$ white blood cells, $4.55x10^6/\mu l$ red blood cells, 13.8 g/dl of haemoglobin and $225x10^3/\mu l$ platelets; creatinine was 0.96 mg/dl while aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 16 U/l and 26 U/l, respectively. Finally, uric acid was 4.7 mg/dl (Table I). According to physical and US examinations, the patient underwent a bilateral radical orchiectomy, as indicated by the European Association of Urology guidelines on testicular cancer, due to the evident tumoral aspect of the testicular masses (7,8). At the surgical table, testes were measured (left testis 10x7x5 cm; right testis 12x8x7 cm) and examined, showing parenchyma completely replaced by whitish-yellow plurinodular and confluent formations (Fig. 1). The subsequent histopathological analysis reported the presence of medium and large size multilobed lymphoid cells, with poor cytoplasm and occasional eosinophilic central nucleoli. No infiltration or congestion of the cord was reported bilaterally. The immunophenotypic profiling revealed a lymphoid proliferation CD 20+, Bcl +/-, CD3- and CD5-, consistent with medium-large cells B-derived non-Hodgkin Lymphoma diagnosis. 18F-FDG PET/CT scan, which was performed in the postoperative staging of the disease, showed multiple avid lesions (>10) located at lungs (SUV max 15.1), pleura (SUV max 11.6), pancreatic head (SUV max 19.4). Nodal involvement comprehended caval (SUV max 4.1), celiac (SUV max 2.3), aortic (SUV max 16.9) and renal (SUV max 15.4) lymph nodes. Finally, several hyperaccumulations were found in the mandibular (SUV max 18.4) and maxillary (SUV max 5.7) region, bilaterally.

Table I. Blood sample values of the patient before surgery.

Value	Result	Normal range
WBC, $x10^3/\mu l$	8.16	4.8-10.8
RBC, $x10^6/\mu l$	4.55	4.2-5
Haemoglobin, g/dl	13.8	12-17.5
Platelets, $x10^3/\mu l$	225	130-400
Creatinine, mg/dl	0.96	0.72-1.25
AST, U/l	16	0-34
ALT, U/l	26	0-55
Uric acid, mg/dl	4.7	3.4-7
LDH, IU/l	348	80-300
AFP, ng/ml	4.13	<6
CEA, ng/ml	4.34	<5
hCG, mIU/ml	2.1	<5
Testosterone, ng/dl	179	350-890

WBC, white blood cells; RBC, red blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; hCG, human chorionic gonadotropin.

A probably reactive hyperaccumulation was found in surgical locations (scrotal and inguinal region) (SUV max 4.4). The patient was subsequently addressed to the haematologist and oncologist for further evaluations. Lumbar puncture was performed to exclude CNS involvement. Skin involvement, after dermatological consultation, was excluded as well, while testosterone replacement therapy was administered with 1,000 mg of intramuscular testosterone undecanoate every 12 weeks.

According to the Lugano Modification of the Ann Arbor staging system, the disease stage was estimated to be IV-E, with a Karnofsky performance status of 100% and ECOG (Eastern Cooperative Oncology Group) grade 0 (9). Deauville criteria score was 2 while International Prognostic Index (IPI) for DLBCL adjusted for age was 2.

The patient underwent to the R-CHOP protocol (rituximab 375 mg/m^2 plus cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 and prednisone 40 mg/m^2) every 21 days for six cycles, as well as 2 cycles of intrathecal methotrexate for CNS prophylaxis. The decision to perform a high-dose chemotherapy and/or haematopoietic stem cell transplantation is still under consideration. The patient is still in follow up, with a current observation time of 5 months, and remain in stable condition, pending subsequent re-evaluation with PET/CT scan.

Discussion

PTL is a rare and extremely aggressive disease, accounting for an annual incidence of 0.26 cases per 100,000 person-years and a median age of presentation of 65 years (10). The staging is similar to other forms of aggressive NHL and is based on the Ann Arbor system, requiring PET/CT with the addition of CNS staging. Considering the particular tropism of this disease for the skin, a thorough examination is required. Among adverse prognostic factors are included: age >70 years, B symptoms (fever, drenching night sweats and loss of >10% of body weight in 6 months), >1 extranodal site, tumour diameter >10 cm and raised LDH (11). Interestingly, despite the large testicles masses reported in our patient, no B symptoms were reported in our case. As reported in the literature, 5-year progression-free survival (PFS) and overall survival (OS) are, respectively, 59.3 and 85%, for patients who underwent a combined protocol including R-CHOP (the treatment of choice for III-E and IV-E Ann Arbor stages), intrathecal chemotherapy and scrotal radiotherapy (1,11). In particular, prophylactic intrathecal chemotherapy and scrotal radiotherapy (in cases of monolateral disease) are indicated in 10-14% of patients considered at high risk (12). Although the approval of rituximab for PTL has been saluted as a potential favourable therapeutic addition, the impact on the outcomes remains unclear (13). Few other similar and recent cases are reported in the literature: Yan *et al* (14) reported the case of a 63-year-old patient with a CNS relapse after a successful treatment of an early monolateral PTL; Sia *et al* (15) reported the case of a younger patient (56-year old) with a right testicular PTL who underwent to scrotal radiotherapy after the R-CHOP protocol and intrathecal methotrexate; Sadiq *et al* (16) reported the case of a 47-year old patients with left PTL; finally Batista and Safriadi (17) reported the case of a bilateral PTL in a 48-year old male, which was treated similarly to our case. Albeit a relatively low testosterone level is reported, PTL is not associated with hypotestosteronaemia, albeit the subsequent treatment could impair the (residual) testicular function. In our case, the bilateral orchiectomy required the administration of testosterone replacement therapy. Few limitations have to be reported in our study. Firstly, we did not have the genetic analysis of the patient; secondly, the follow-up is still ongoing and further clinical decision could be further made.

In conclusion, PTL is a rare and aggressive disease, characterized by a poor prognosis. Despite being traditionally reported in patients over 60 years, as reported in our case, it could be seen also in younger patients, with an aggressive and metastatic and bilateral presentation at the time of the diagnosis. Its rare incidence and the peculiar behaviour of the malignancy have made difficult a standardized approach. Considering the particular tropism to CNS, skin and contralateral testis, a careful and thorough patient's evaluation is required, utilizing a multidisciplinary approach in order to overcome the difficulties of this disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DDD, BB, LN, FC and VV wrote and reviewed the manuscript. DDD, ARZ, DDB, GN and VV performed surgical treatment and related post-operative follow up of the patient. ARZ, GN, DDB, PR and LDL supervised the study. BB, LN, FC, PR, LDL, IS, CA, LC and GMF conceived the study, collected the data and verified the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent for participation was obtained from the patient. Ethics approval was not required due the retrospective nature of the work and the absence of procedure performed outside the normal clinical practice.

Patient consent for publication

Written informed consent for publication of the case and related images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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