Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Unusually aggressive primary testicular diffuse large B-cell lymphoma initially presenting as systemic disseminating metastases in older adult men: a case report

Kuang-Ting Liu, MT, MS[a,b], Yueh-Ching Chang, MT, MS[a,e], Yu-Chieh Lin, MD[a,d], Junn-Liang Chang, MD, PhD[a,c,d,e,*]

Introduction: Primary testicular lymphoma (PTL) accounts for 1–2% of all nonHodgkin lymphomas (NHL), 4% of extranodal nonHodgkin lymphomas, and ~9% of testicular malignancies. A rare subtype of PTL is primary testicular diffuse large B-cell lymphoma (PT-DLBCL), which may initially present as disseminating metastasis in older adult males and has a poor prognosis.
Case presentation: Herein, the authors describe the case of a 64-year-old man with the chief complaint of a painless unilateral scrotal mass. Computed tomography scans of the abdomen and a pelvic examination demonstrated a left testicular tumor with multiple lymphadenopathies partially aggregated in the para-aortic area and disseminated to multiple soft tissues and organs. Subsequently, the patient underwent a left radical orchiectomy. Pathological and immunohistochemical examinations confirmed the diagnosis of left PT-DLBCL with systemic disseminating metastases.
Clinical discussion: PTL often aggressively spreads to other extranodal organs, such as the contralateral testis, central nervous system, lung, pleura, Waldeyer's ring, and soft tissues. In men over 60 years of age, PT-DLBCL is the most common testicular malignancy. However, extensive systemic metastasis as the initial presentation is extremely rare. PT-DLBCL has a dismal prognosis and requires radical orchiectomy followed by multimodal therapy and central nervous system prophylaxis or systemic intervention to improve survival.
Conclusion: The diagnosis of PT-DLBCL through preoperative and imaging examinations is often challenging. Thus, histopathology and immunohistochemical markers play a crucial and valuable role in the definite diagnosis and differential diagnosis of PTLs.

Keywords: diffuse large B-cell lymphoma, immunohistochemical staining, nonhodgkin lymphoma, orchiectomy, primary testicular lymphoma

Introduction

Primary testicular lymphoma (PTL), which accounts for ~9% of all testicular malignancies and ~1–2% of all nonHodgkin lymphomas, is the most common testicular malignancy in older adult males[1–5]. It is a rare and aggressive extranodal lymphoma. Primary testicular diffuse large B-cell lymphoma (PT-DLBCL) is a unique subtype of diffuse large B-cell lymphoma (DLBCL) and is the most common histological type of PTL, usually diagnosed at 66–68 years of age. The disease exhibits aggressive clinical behavior and relatively high relapse rates as the most common bilateral testicular tumor[5–9]. PTL often spreads to other extranodal organs, such as the contralateral testis, central nervous system (CNS), lung, pleura, Waldeyer's ring, soft tissues, and

HIGHLIGHTS

- Primary testicular diffuse large B-cell lymphoma (PT-DLBCL) is a rare, aggressive subtype of extranodal nonHodgkin lymphomas. Disseminating metastasis is extremely rare in this subtype.
- PT-DLBCL has unique biological characteristics and requires treatment modalities with systemic intervention at an early stage.
- Radical orchiectomy followed by chemotherapy is the best recommended therapeutic option.
- The final diagnosis of PT-DLBCL must be obtained by resection of the testicular tumor and through pathologic and immunohistochemical examination.

[a]Department of Pathology and Laboratory Medicine, Taoyuan Armed Forces General Hospital, [b]Hsin Sheng Junior College of Medical Care and Management, [c]Taipei Veterans General Hospital Taoyuan Branch, [d]Department of Biomedical Engineering, Ming Chuan University, Taoyuaan City and [e]Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei City, Taiwan

K.T.L. and Y.C.C. contributed equally to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Pathology and Laboratory Medicine, Taoyuan Armed Forces General Hospital, Taoyuan City, Taiwan. 32551, No.168, Zhongxing Rd., Longtan Dist., Taoyuan City, Taiwan. Tel.: 886 3 4799595 325571; Fax: 886 3 4809946. E-mail: junn9liang@yahoo.com.tw (J-L. Chang).

Annals of Medicine & Surgery (2023) 85:4106–4111

Received 9 May 2023; Accepted 10 June 2023

Published online 28 June 2023

http://dx.doi.org/10.1097/MS9.0000000000001018

prostate, but less frequently into the kidney, liver, bone marrow, pleura, and bone[7,9–11].

The most common clinical symptom is the painless swelling of the scrotum. Testicular ultrasonography with orchiectomy, as well as histology and immunohistochemistry, are the most important tools for diagnostic evaluation[1,10,12]. To our knowledge, the present case is the first to describe an unusually aggressive PT-DLBCL that initially presented with systemic disseminated metastases in an adult male. This case report has been reported in accordance with the Surgical CAse REport (SCARE) 2020 criteria[13].

Case presentation

A 64-year-old man presented with a painless, progressive enlargement of the left testis of 3 months duration. No associated B symptoms (e.g. fever, night sweats, and unintentional weight loss) were experienced before admission. As the mass was painless, the patient ignored it and did not seek any treatment until the mass grew in size.

On admission, the patient's vital signs were stable (body temperature: 37.2°C, heart rate: 106/min, respiratory rate: 18-/min, blood pressure:130/80 mmHg). The patient's past medical, occupational, and travel history were unremarkable. He denied a history of consuming alcoholic beverages and illegal drugs and had no known drug allergies and/or adverse reactions. Moreover, there was no contributing family history, including no relevant genetic information and psychosocial history.

On clinical examination, the patient was afebrile. A painless solid left testicular mass inseparable from the testis was palpated. The right testis was unremarkable. No palpable centimetric left inguinal lymph nodes were noted.

Clinical laboratory abstracted analysis including a complete blood count revealed mild leukocytosis with neutrophilia and a normal lymphocyte count (hemoglobin: 11 g/dl, hematocrit: 33%, white blood cells: 14.3×10^3 u/l, lymphocytes: 4.0%). The biochemistry analysis showed C-reactive protein levels of 5.97 mg/dl (normal <0.5), blood urea nitrogen levels of 33.5 mg/dl (normal: 6 – 24), and glucose levels of 125.7 mg/dl (normal: 70 – 110). Microcytic anemia was highly suspected. Urine trace proteins were noted. Of all testicular tumor markers measured, carcinoembryonic antigen, alpha-fetoprotein, and human chorionic gonadotropin were within the normal range. However, lactate dehydrogenase (LDH) was elevated at 565 U/L (normal 135 – 225). Biomarker serum levels of carbohydrate antigen19-9, carbohydrate antigen 125, squamous cell carcinoma antigen, and cardiac markers NT-proBNP were within normal limits. All serological evaluations were negative, particularly for HIV, hepatitis C virus, Epstein-Barr virus, and coronavirus disease 2019.

Scrotal examination revealed an enlarged firm mass about 7×4 cm affecting the left testis. In contrast, the right testis was normal in contour. Chest radiography results were clear of lung metastasis. Ultrasonography examination revealed a semisolid spongiform mass in the left testicle, suggestive of malignancy, and hydrocele formation. Further computed tomography (CT) scan of the chest, abdomen, and pelvis demonstrated an ill-circumscribed left testicular mass with multiple lymphadenopathies partially aggregated in the para-aortic area with dissemination to multiple organs and soft tissue involvement (Fig. 1A-B). Consequently, the patient was diagnosed with a left testicular tumor and suspected primary lymphoma of the testis with hydrocele and disseminated intra-abdominal lymphadenopathies. The right testis was unremarkable. The patient subsequently underwent a left radical orchiectomy by a senior attending urologist and had an uneventful postoperative course without complications.

Histopathological examination

Macroscopic examination of the radical orchiectomy specimen showed an enlarged testicle, homogenously yellowish-tan with a lamellar semisolid spongiform mass measuring $7 \times 4 \times 3.8$ cm with multifocal hemorrhages and necrosis attached to the spermatic cord (no gross shown). A hydrocele was also found.

Microscopically, the testicular parenchymal tumor was completely replaced by a monomorphic tumor lymphocyte population exhibiting a diffuse growth pattern. Tumor cells had diffusely infiltrated the tissue space, producing extensive separation of the intact seminiferous tubules. Spermatogenic arrest, interstitial fibrosis, and marked tubular hyaline degeneration were also detected. Discohesive tumor cells composed of uniform moderate-to-large lymphocytic proliferation with hyperchromatic, pleomorphic nuclei with active mitotic figures, and prominent nucleoli (Figs. 2A, B) were observed.

In some areas, the vascular and tubular walls were destroyed as the lumen invaded. Subsequent immunohistochemical (IHC) staining demonstrated that neoplastic cells were positive for the B-lymphocyte antigen, CD45. Moreover, pan-T (CD3) highlighted reactive T-cells. Pan-B-cell antigen expression included diffusely positive immunoreactivity for CD20 (Fig. 3A), CD79a, and increased proliferative Ki-67 labeling index expression in ~85 – 90% of affected tumor cells (Fig. 3B). Tumor cells were also positive for multiple myeloma oncogene 1, postgerminal center or activated B-like (MUM-1/ IRF) (Fig. 3C), Bcl-2 (Fig. 3D), and scattered positive for Bcl-6 (B-cell lymphoma 6, germinal center marker). In contrast, they were negative for CD3, CD5, CD30, Bcl-6, CD-10 (germinal center marker), pan-CK, EMA (epithelial membrane antigen), calretinin (for mesothelial cell), NSE, cyclin-D1, and CD138 expression. The IHC result was diffuse strong immunostaining for CD45, CD20, MUM-1, and Ki-67 indicated the diagnosis of PT-DLBCL with a nongerminal center B-cell-like phenotype. The histopathological and IHC examinations confirmed primary DLBCL of the left testis.

Compared to presurgical levels, testicular tumor markers postorchiectomy showed a significantly lower LDH level of 322 U/L. The postoperative course was uneventful and the patient was discharged two days after surgery, and was referred for chemotherapy. After further consultations with oncologists, the disease was tentatively staged as advanced despite the absence of B symptoms. The revised International Prognostic Index for DLBCL was four at least. A bone marrow biopsy was recommended. However, the patient refused further biopsy examinations and further chemotherapeutic intervention. Written informed consent was obtained from the patient for this case report. Unfortunately, the patient was lost to follow-up after 6 months postsurgery. The patient eventually died according to a telephone interview with his family.

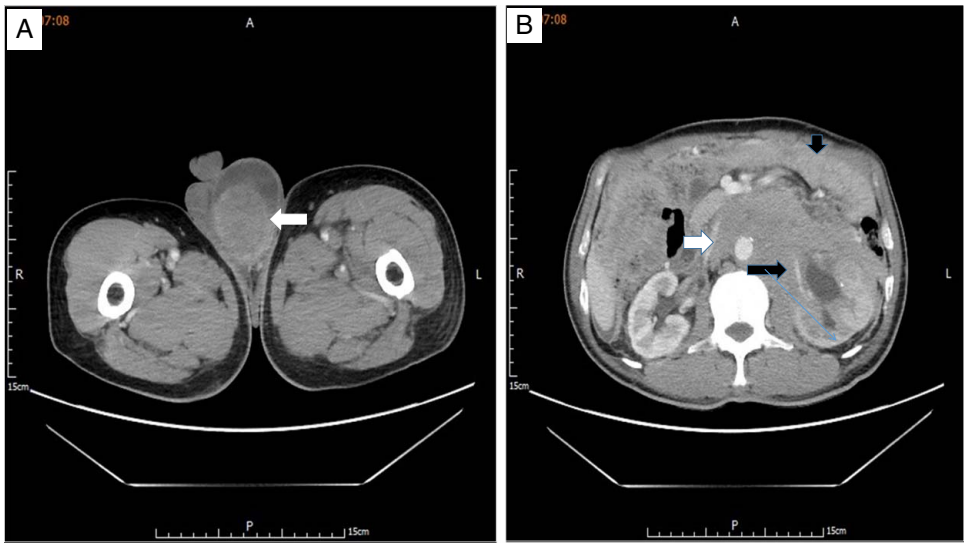

Figure 1. Computed tomography scans of the lower abdomen and pelvis shows a (A) left testicular ill-circumscribed mass (white arrow) (B) with multiple lymphadenopathic aggregation in the para-aortic area (white arrow), disseminated to multiple organs, left kidney (red arrow), and has soft tissue involvement (yellow arrow).

Discussion

PTL is a rare type of lymphoma while its subtype, PT-DLBCL, is a rare and aggressive mature B-cell lymphoma that commonly occurs in older adult men. Most PTLs are diffuse large B-cell types with the potential for aggressive clinical behavior[5,7,13]. DLBCL is the most common primary histology. Other aggressive histologies, especially Burkitt lymphoma, are prevalent in secondary testicular involvement with unilateral or bilateral testicular manifestations with a propensity to invade the CNS and have a poor prognosis[4,6,8,9,11].

PT-DLBCL has a high morbidity and mortality rate. Its clinical manifestations include a unilateral testicular painless mass, occasionally accompanied by mild scrotal pain and a suspected hydrocele or testicular tuberculosis. Associated B symptoms are rarely reported, and it can easily be misdiagnosed as seminoma or orchitis[1,3,5].

The median age of affected patients is older (64 years) as was our case. In advanced patients, 25 – 41% developed systemic B symptoms (i.e. fever, night sweats, and weight loss). PTL is also considered to be the most common bilateral testicular cancer, with a 35% incidence of metachronous bilateral testes, and a 3% incidence of synchronous testicular involvement. In most PTL cases, unilateral or bilateral testicular masses indicate local involvement[14]. In more advanced stages, as in our case, significant para-aortic lymph node involvement and abdominal pain

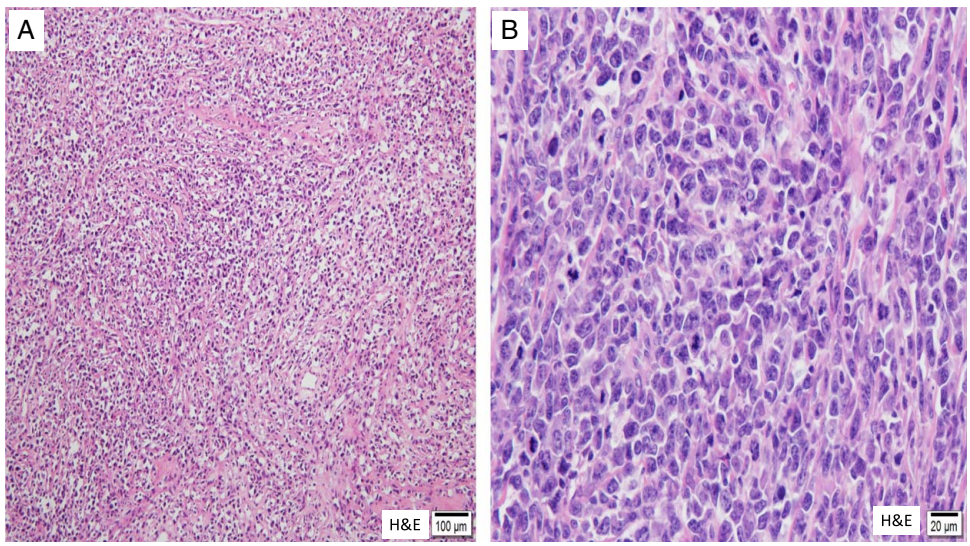

Figure 2. Photographs of PT-DLBCL of the left testis illustrate (A) the predominance of a population of large lymphoma cells (H&E stain, original magnification × 100) (B) and active abnormal mitoses (H&E, original magnification × 400).

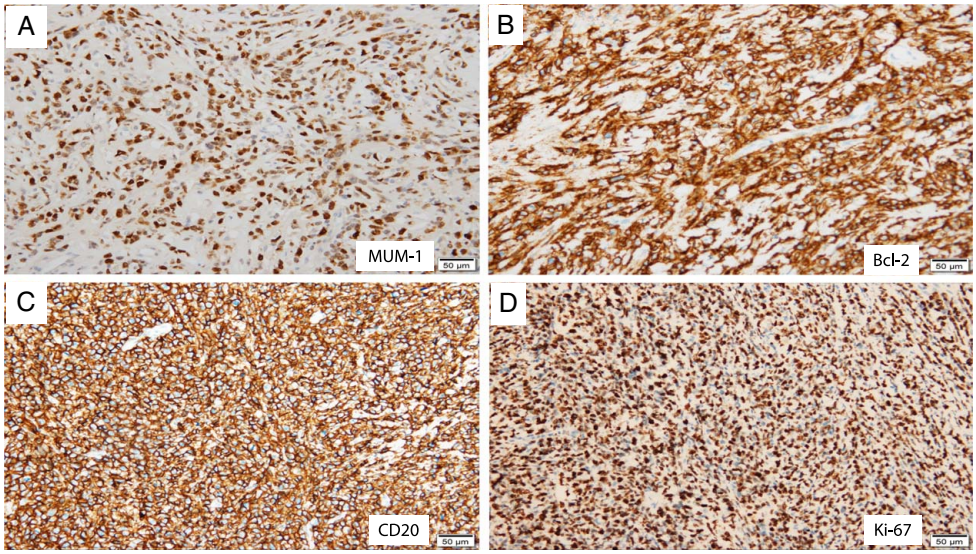

Figure 3. Immunohistochemical (IHC) analysis of representative sections of the PT-DLBCL specimen are diffusely positive for MUM-1 (A, IHC, original magnification × 200), Bcl-2 (B, IHC, original magnification × 200) CD20 (C, IHC, original magnification × 200) and a proliferative Ki-67 labeling index activity in ~90% of lymphoma cells (D, IHC, original magnification × 200).

are evident. Testicular lymphoma often disseminates to other extranodal organs, such as the contralateral testis, CNS, lungs, pleura, Waldeyer's ring, and soft tissue[1,3,5,10,12].

Little is known about the etiology and pathogenesis of PT-DLBCL. HIV infection may increase PT-DLBCL risk in younger patients, causing genetic aberrations leading to oncogenic signaling, NF-κB pathway activation, and immune-escape phenotypes[8,13,15]. In our present case, extensive metastasis and a left testicular mass were seen without evidence of previous lymphoma, reported B symptoms, and elevated LDH levels but its genetic profile is unknown. The molecular and clinical features of PT-DLBCL may provide information on the unique aspects of this organotypic lymphoma to guide rational therapeutic strategies[10,12].

The exact extranodal sites of PTL dissemination remain unclear but often include the CNS, contralateral testis, kidney, adrenal gland, maxillary sinus, and soft tissue, similar to other studies. Potential explanations include: the efficacy of chemotherapy is decreased in the CNS and contralateral testis due to the blood brain barrier and blood-testis barrier; integrin and adhesion molecules are poorly expressed in PTL resulting in poor adhesion of tumor cells to the extracellular matrix; the CD44 variant plays significant roles in lymphoma dissemination.

To our knowledge, this is the first case to describe an unusually aggressive PT-DLBCL that initially presented with systemic disseminated metastases in an adult male.

The diagnosis is based on history taking, physical examination, ultrasonography, CT, and MRI. HIV serology should also be performed as it has a high concurrency with nonHodgkin lymphoma[2,14,15] In our case, a CT scan revealed a testicular mass with hydrocele, multiple metastases, and the involvement of paraaortic lymph nodes along with masses in the liver, abdominal cavity, and soft tissue without ascites. No abnormalities were found in the contralateral testis and CNS. Imaging of tumor metabolism using FDG PET/CT for the initial staging, follow-up, treatment response monitoring and assessment of disease relapse in lymphomas has become a valuable molecular technique[8]. Testicular tumor markers should be obtained before histopathological result are available[1,7,10]. Compared to presurgical results, the patient's testicular tumor marker showed normal alpha-fetoprotein and ß-human chorionic gonadotropin levels but decreased serum LDH levels postsurgery. A bone marrow biopsy is needed to assess possible lymphoma involvement but can be omitted if a PET-CT-scan demonstrates bone disease[1,2,14].

Differential diagnoses of primary testicular DLBCL may include germ cell tumors such as classic seminoma, and embryonal carcinoma. The vast majority of PTLs are approximately 80 – 98% DLBCL, although HIV-infected patients often display more aggressive variants. Histopathological characteristics of PT-DLBCL typically expresses B-cell markers include the CD19, CD20, CD79a, and PAX5. Approximately 70% of cases express the Bcl-2 protein but are rarely positive for Bcl-6. The median proliferative Ki-67 labeling index is higher, and the Epstein-Barr virus test is usually negative in non-HIV populations[2,3,8]. Histopathology plays a key role, and IHC markers are of high value in the definite and differential diagnosis of tumors[10,14].

Treatment of patients with primary testicular DLBCL can be divided into limited disease (stage I/II) and advanced disease (stage III/IV) treatment. For limited disease, no standard treatment has been established to prevent a possible relapse in the contralateral testis and the CNS[8,16]. Orchiectomy provides histological diagnosis and removes potential sanctuary sites, as the blood-testicular barrier renders testicular tumors intractable to systemic chemotherapy[1,15,16]. Thus, orchiectomy followed by chemotherapy (CHOP or CHOP-like regimens), local R/T and preventive CNS intrathecal injection are widely accepted options[2]. In more advanced or relapsed disease, management should follow the worldwide recommendations for nodal DLBCL[4,6,10,12,15]. The majority of PT-DLBCL cases have limited stage disease with lymphoma localized in the testis (stage IE). Approximately 20% have locally-advanced stage II disease, whereas disseminated stage IV disease is virtually indistinguishable from a nodal DLBCL with testicular involvement[1,10,12,16].

Prognostic factors for progression-free survival identified in PTL include age greater than 70 year, advanced stage with a disseminated disease with testicular involvement, B symptoms, ECOG performance status, greater than 1 extranodal site, involvement of extranodal sites other than the testis, tumor diameter greater than 10 cm, raised serum LDH, markers of high tumor burden, and disseminated disease[2,3,7,12,16]. It has been reported that they were associated with good performance status, limited stage, low IPI score, absence of B symptoms, normal serum LDH, and β2-microglobulin, absence of additional extranodal sites involvement, and right testis involvement[6]. Limited Ann Arbor stage, further chemotherapy following orchiectomy, and a low IPI score (< 2) are correlated with superior survival for DLBCL patients. Thus, systemic treatments, include radical orchiectomy, chemotherapy, radiotherapy, and intrathecal prophylaxis, are necessary for all patients with PTL. The prognosis of patients with PTL who experience relapses is poor. Relapses are frequent despite aggressive treatment. Patients with relapsed PTL have a poor prognosis, with a median survival of 4.5 to 10 months[10]. In stage I–II disease, median survival is about 6 years, and in stage IV disease, it is only 5 months[12,15]. The time to disease progression also differs, with a median time to recurrence/progression of 36 months for stage I–II patients and 5 months for stage IV patients[2,12,14,15].

Our patient received a pathology report which was thoroughly explained to him and his family. The patient refused a liver and bone marrow biopsy and further chemotherapy. Ultimately, the patient was lost to follow-up and died.

We first report an unusually aggressive PT-DLBCL initially presenting as systemic disseminating metastases with malignant pleural effusion in an older adult male, confirming that PTL is an aggressive disease with a poor prognosis.

Conclusion

PT-DLBCL is characterized by its low incidence, high aggressiveness, dismal prognosis, and complicated therapeutic approach. Histopathology and IHC markers play an important role and has high value in the definite diagnosis and differential diagnosis of PTLs. A multidisciplinary team and systematic interventions need to be actively considered in the early stages of PTL to obtain a better prognosis.

Ethical approval

Institutional Review Board Statement: This study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH), National Defense Medical Center. The reference: IRB approval No. is TSGHIRB No: B202315026.

Consent of Patient

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

This study was supported by grants from TYAFGH-A-112011 and TYAFGH-A-112014, Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan.

Author contribution

J.-L.C.: drafting manuscript review, corresponding author, data interpretation, evaluation, information acquisition, and final approval; K.-T.L.: responsible for operating pathological tissue-/specimen processing, information acquisition and final approval, concept and design, critical review, and final approval; Y.-C.C.: responsible for operating pathological tissue sections, special chemical staining and immunohistochemical staining, information acquisition, critical review, and final approval; Y.-C.L.: responsible for information acquisition and final approval, concept and design, critical review and final approval.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

This paper is a case report; there was no registration. The datasets in this article are available in the Department of pathology and Laboratory Medicine database, upon request, from the corresponding author.

Guarantor

The guarantor is that individual who accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Data availability statement

Not applicable to this article.

Provenance and peer review

Not commissioned, externally peer reviewed.

Acknowledgements

The authors like to thank Dr Yen-Lin Chen, Department of Radiology, for providing the medical images and explanations of the present case. The authors also like to thank to Dr Zheng-Lia Gao, Department of Surgery, for explaining the intraoperative findings. The authors are also grateful to Mei-Ling Li, medical laboratory technician, for assisting in pathological sectioning and processing IHC and histochemical staining.

References

[1] Vitolo U, Ferreri AJ, Zucca E. Primary testicular lymphoma. Crit Rev Oncol Hematol 2008;65:183–9.
[2] Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. Blood 2014;123:486–93.
[3] Lokesh KN, Sathyanarayanan V, Kuntegowdanahalli CL, *et al*. Primary diffuse large B-Cell lymphoma of testis: a single centre experience and review of literature. Urol Ann 2014;6:231–4.
[4] Deng L, Xu-Monette Z, Loghavi S, *et al*. Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era: a report from the International PTL Consortium. Leukemia 2016;630:361–72.

[5] Wang Q, Zheng D, Chai D, *et al*. Primary testicular diffuse large B-cell lymphoma: case series. Medicine (Baltimore) 2020;99:e19463–672.
[6] Chen B, Cao DH, Lai L, *et al*. Adult primary testicular lymphoma: clinical features and survival in a series of patients treated at a high-volume institution in China. BMC Cancer 2020;20:220–30.
[7] Batista B, Safriadi F. Bilateral primary testicular diffuse large B-cell lymphoma: a case report. J Surg Case Rep 2021;2021:1–3.
[8] Hermi A, Bibi M, Rahoui M, *et al*. A case report of testicular diffuse large B-cell malignant lymphoma with cutaneous metastasis: a rare entity. Int J Surg Case Rep 2021;88:106519–22.
[9] Pollari M, Leivonen SK, Leppä S. Testicular diffuse large b-cell lymphoma-clinical, molecular, and immunological features. Cancers (Basel) 2021;13:4049–66.
[10] Goel S, Sachdev R, Mohapatra I, *et al*. Unusually aggressive primary testicular diffuse large b cell lymphoma with post therapy extensive metastasis. J Clin Diagn Res 2016;10:ED01-2.
[11] Yan Z, Yao S, Wang Y, *et al*. Primary testicular lymphoma with central nervous system relapse was successfully treated by a chemo-free regimen: a case report and literature review. Cancer Manag Res 2021;13:9489–500.
[12] Koukourakis G, Kouloulias V. Lymphoma of the testis as primary location: tumour review. Clin Transl Oncol 2010;12:321–5.
[13] Agha RA, Franchi T, Sohrabi C, *et al*. SCARE Group. The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2020;84:226–30.
[14] Trama F, Illiano E, Aveta A, *et al*. Bilateral primary testicular diffuse large B-CELL lymphoma. Urol Case Rep 2021;38:101733–6.
[15] Guo D, Hong L, Ji H, *et al*. The Mutation of BTG2 gene predicts a poor outcome in primary testicular diffuse large B-Cell lymphoma. J Inflamm Res 2022;10:1757–69.
[16] Twa DDW, Mottok A, Savage KJ, *et al*. The pathobiology of primary testicular diffuse large B-cell lymphoma: implications for novel therapies. Blood Rev 2018;32:249–55.