Case Series

Case series of primary testicular lymphoma: Insights into a rare condition

Kiran G Chaudhary[1], Amruta Tripathy[2], Puneet Kumar Bagri[3], Himanshi Avinash Jain[4]

From [1]2nd-year Resident Doctor, [2]Consultant Radiation Oncologist, [3]Senior Consultant and Head, [4]Consultant Radiation Oncologist, Department of Radiation Oncology, Shree Krishna Hospital and Medical Research Centre, Karamsad, Gujarat, India

ABSTRACT

Primary testicular lymphoma (PTL) is a rare extranodal type of non-Hodgkin's lymphoma (NHL), accounting for <5% of testicular malignancies and 1–2% of NHL cases. The most common PTL is diffuse large B-cell lymphoma (DLBCL) type, a highly heterogeneous form of NHL, with a higher incidence in men over 60. Testicular lymphoma frequently recurs in extranodal sites, especially the contralateral testis and central nervous system (CNS), which is a sign of poor prognosis. Given the aggressive nature of testicular DLBCL, multimodal management is required, including orchiectomy, immunochemotherapy with rituximab, contralateral testicular radiation, and CNS prophylaxis to improve outcomes. In this case series, we present two cases of PTL, both diagnosed through histopathology and imaging and treated with a combination of surgery, chemotherapy, and radiation therapy.

Key words: Diffuse large B-cell lymphoma, Non-Hodgkin's lymphoma, Primary testicular lymphoma

Primary testicular lymphoma (PTL) is a rare form of extranodal non-Hodgkin's lymphoma (NHL). Extranodal NHL accounts for <5% of testicular malignancies and 1–2% of all cases of NHL [1]. Men over 60 are more likely to develop testicular NHL [2]. Pathologically, 80–98% of PTL is diffuse large B-cell lymphoma (DLBCL), the most common and one of the most heterogeneous types of NHL. Around 20% of cases involve bilateral instances [1]. Testicular-DLBCL arises primarily in the immune-privileged site of the testis and represents the most commonly activated B-cell-like or non-germinal center B-cell (GCB)-like phenotype [3]. It has a high tendency to relapse in other extranodal sites, typically the contralateral testis and the central nervous system (CNS), and especially relapses of the CNS, are associated with poor prognosis [4]. The standard treatment scheme is orchiectomy of the disease-involved testis, immunochemotherapy combined with rituximab, contralateral testicular radiation therapy, and CNS prophylaxis with intrathecal (IT) or intravenous methotrexate (MTX) [5].

PTL is a rare and unique type of malignancy. Over the past 60 years, approximately 1,600 cases have been reported worldwide, highlighting its rarity and limited insights [9,15] (Table 1).

CASE SERIES

Case 1

A 71-year-old male presented with a complaint of painless swelling over the left testis for 2 months. The patient underwent a computed tomography (CT) scan of the thorax, abdomen, and pelvis, revealing a large enhancing mass lesion in the left scrotal sac measuring 94 × 60 × 112 mm. Bilateral inguinal lymph nodes with preserved fatty hilum were noted, with the largest node on the right side measuring 10.5 × 7.1 mm, and on the left side measuring 12.5 × 7.1 mm. Additionally, tiny small nodes were observed along the right external iliac vessels, the largest measuring 6 × 9.5 mm (Fig. 1).

The patient then underwent left high inguinal orchidectomy, and histopathology revealed a 12 × 7 × 6 cm B-cell NHL extending into the spermatic cord and surrounding fat, with lymph vascular invasion present (Fig. 2). Immunohistochemistry (IHC) indicated DLBCL, GCB type, positive for CD20, c-Myc, BCL2, CD10, BCL6 (Fig. 3), and negative for CD3, CD5, with Ki-67 index at 70%. Hence, based on histopathological and radiological investigations, the patient was staged IA. The patient presented to the outpatient department after a left high inguinal orchidectomy. The patient was conscious, oriented, and appeared well-nourished. He had no signs of pallor, edema, cyanosis, or icterus on general examination. His vitals were as follows: temperature was normal by touch, blood pressure was 122/78 mmHg, pulse was 78/min, respiratory rate was 16/min, and SpO_2 was 98% on room air. On inspection and palpation, the left side orchidectomy status and postoperative scar were seen in the inguinal region, and the right side scrotum was normal: No abnormality was seen. On follow-up, the patient underwent 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, which showed post-high inguinal orchidectomy status with no distant metastasis.

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Correspondence to: Amruta Tripathy, Department of Radiation Oncology, Shree Krishna Hospital, Karamsad, Gujarat, India. E-mail: amrutatripathy4u@gmail.com

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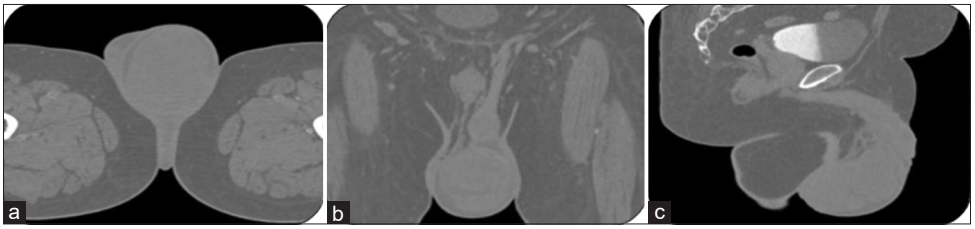

Figure 1: Computed tomography scan images showing a large enhancing mass lesion in the left scrotal sac. Bilateral inguinal lymph nodes with preserved fatty hilum are noted, with the largest node on the right side. (a) Axial view, (b) Coronal view, (c) Sagittal view (Case 1)

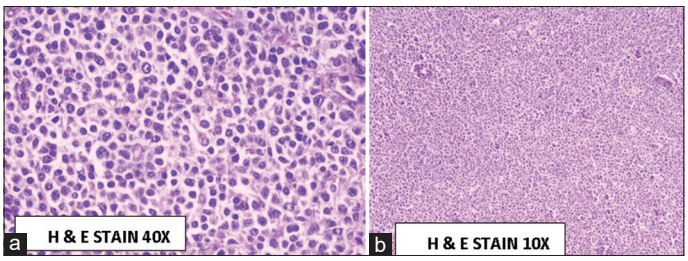

Figure 2: (a and b) The sections show complete effacement of testicular parenchyma medium to large atypical lymphoid cells. The cells have round to oval, vesicular nuclei with it is diffusely infiltrated by prominent nucleoli and scant eosinophilic cytoplasm. Atypical mitosis with focal areas of necrosis noted. (H and E: hematoxylin and eosin stain) (Case 1)

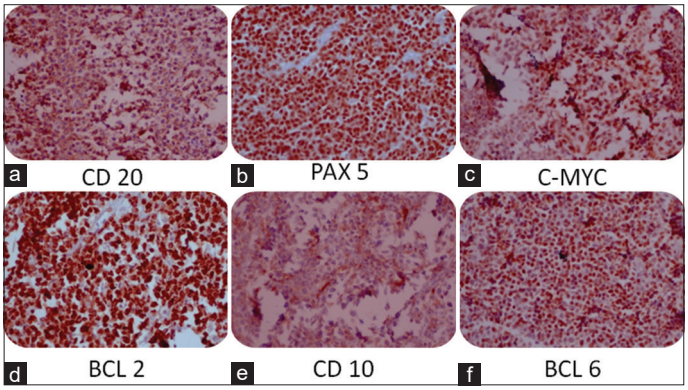

Figure 3: (a-f) Immunohistochemistry of orchidectomy specimen showing positivity for CD 20, PAX 5 (B cell marker), C-MYC, BCL-2, CD 10, and BCL 6 for diffuse large b cell lymphoma, germinal center B-cell like of left testis (Case 1)

Based on the histopathological examination and radiological imaging, the patient was planned for curative chemotherapy and received four cycles of R-CHOP + IT MTX (Rituximab 375 mg/m^2 + cyclophosphamide 750 mg/m^2 + Doxorubicin 50 mg/m^2 + Vincristine 1.4 mg/m^2 + Prednisolone 100 mg + MTX 12 mg IT) till November 2024 and now planned for contralateral testis irradiation.

Case 2

A 64-year-old male, with a known case of testicular DLBCL, presented with a complaint of swelling over the left testis for 2 months. The patient underwent several investigations, including an ultrasound of the testis, which revealed a 5.5 × 4.5 × 2.3 cm hypoechoic area with increased vascularity in the left testis, suggestive of malignancy. A CT of the thorax, abdomen, and pelvis showed a 54 × 29 × 45 mm well-defined enhancing hypodense lesion in the left testis, suggestive of a testicular mass, with no evidence of inguinal lymphadenopathy but a few subcentimeter-sized para-aortic nodes seen, the largest measuring 12 × 10 mm (Fig. 4a-c).

The patient then underwent a left high inguinal orchidectomy, and histopathological examination revealed a 6.0 × 5.0 × 4.5 cm mass of NHL with no spermatic cord invasion, confirmed as DLBCL. IHC showed positivity for CD20, C-MYC, MUM-1, and CD10 and negativity for BCL-2 and CD5, with a Ki67 index of 80%, confirming the diagnosis of DLBCL, GCB type. The patient presented to the outpatient department after a left high inguinal orchidectomy. The patient was conscious, oriented, and appeared well-nourished. He had no signs of pallor, edema, cyanosis, or icterus on general examination. His vitals were as follows: temperature was normal by touch, blood pressure was 110/82 mmHg, pulse was 82/min, respiratory rate was 16/min, and SpO_2 was 98% on room air. On inspection, palpation of left-side orchidectomy status and the postoperative scar was seen, and the right-side scrotum was normal; no abnormality was seen. On a follow-up, the patient underwent FDG PET/CT that showed post-left high inguinal orchidectomy status, with low-grade FDG uptake noted in the ill-defined soft tissue in the postoperative bed in the left testicular region, measuring 1.6 × 1.5 cm with an SUVmax of 4.41. On the basis of histopathological examination and radiological imaging, the patient was planned for curative chemotherapy four cycles of R-CHOP + IT MTX followed by two cycles of Rituximab (Rituximab 375 mg/m^2 + cyclophosphamide 750 mg/m^2 + Doxorubicin 50 mg/m^2 + Vincristine 1.4 mg/m^2 + Prednisolone 100 mg + MTX 12 mg IT) and then will be planned for contralateral testis irradiation.

DISCUSSION

In NHL, DLBCL is the most common subtype in terms of incidence and overall, in NHL. Worldwide, DLBCL accounts for one-third of all NHLs. According to the cancer registry data from the U.S., the age-standardized rate of incidence for DLBCL is 7.2/100,000. DLBCL incidence increases with age and is generally higher in males than in females; in the U.S., the highest incidence is observed among non-Hispanic whites (9.2/100,000) [6].

Lymphomas usually present as a solid mass arising in lymph nodes and extranodal sites anywhere in the body, primarily involving lymphatic tissue such as the bone marrow, spleen, and thymus in many cases. Lymphoma has a tendency to spread to

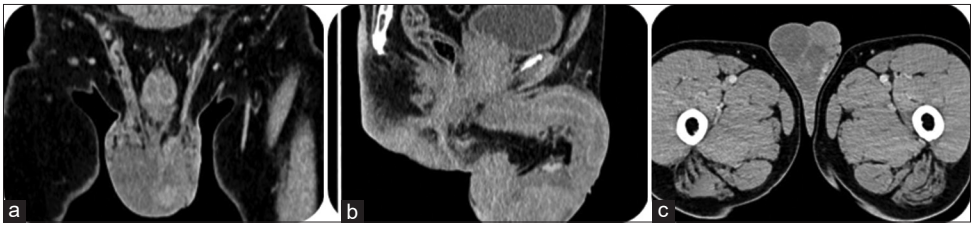

Figure 4: Computed tomography scan images showing a well-defined enhancing hypodense lesion in the left testis, suggestive of a testicular mass, with no evidence of inguinal lymphadenopathy (a) Coronal view, (b) Sagittal view and (c) Axial view (Case 2)

Table 1: The review of the literature concerning histology and treatment

Study/year	Number and duration of study	Histology	Treatment	CNS prophylaxis
Wang *et al*. [10] 2013	2001–2012 n=13 PTL-13 DLBCL-9	DLBCL/NHL B cell type/T cell type	Orchiectomy- all RT-1 CT-4	3
Vitolo *et al*. [5] 2011	Phase II trial 2001-2006 n=53	Stage I or II PTL	Orchiectomy- all RT-47 CT-all (R-CHOP21)	50
Gupta *et al*. [12] 2009	2002–2008 n=6 PTL-6 DLBCL-5	DLBCL/NHL	Orchiectomy- 4 RT-1 CT-6	3- Prophylactic cranial RT IT MTX-6
Lantz *et al*. [13]	1992–2005 n=12 DLBCL-11 ALCL-1	DLBCL/ALCL	Orchiectomy- all, RT-7 CT-7	IT MTX-3 Cranial RT-1 Scrotal RT-5
Darby and Hancock [14] 2005	1972–2002 n=30	NHL	Orchiectomy- all RT- 7, CT- 15	none
Zhang *et al*., 2024 [15]	Systematic review and meta-analysis of multiple studies 22 articles, n=475	Diffuse Large B-cell lymphoma (DLBCL), 95.5% cases; Non-GCB subtype 69.3%	Orchiectomy + chemotherapy (76.7% in related studies), radiotherapy (36.7%), multimodal therapy (33.3%)	CNS prophylaxis Given.
Xu and Yao, 2019 (SEER Analysis, 1973–2013) [9]	1,169 cases	82.9% DLBCL 88.7% B-cell NHL 1.3% T-cell NHL	chemotherapy, radiotherapy+Orchiectomy (diagnostic and therapeutic)	CNS prophylaxis given

ALCL: Anaplastic large cell lymphoma, CT: Chemotherapy, CR: Complete remission, DLBCL: Diffuse large B cell lymphoma, IT MTX: Intrathecal methotrexate, N: Number, NHL: Non-Hodgkin's lymphoma, PTL: Primary testicular lymphoma, RT: Radiotherapy, R-CHOP: Rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone, Non-GCB: non-germinal centre B-cell

extranodal sites or locations other than lymphatic organs, with or without related nodal involvement; this can be primary or secondary to hematogenous spread from the nodal site to the extranodal site. Extranodal involvement is more commonly observed in NHL (25–40% higher) than in Hodgkin lymphomas whereas relatively less common around 1–2%. In NHL around one-third of cases originate from locations outside of the lymph nodes, spleen, or bone marrow [7].

Amongst extranodal sites, the gastrointestinal tract is the most common site, accounting for around 43%, followed by head and neck in 14%, skin 7%, brain 6–7%, bone 5%, and lung (2%) [8]. The incidence of PTL is 1–9% of all testicular malignancies and 1–2% of NHLs and it is an example of a very rare extranodal lymphoma. The annual incidence is 0.09–0.26/100,000 individuals. In PTL, DLBCL is the most common subtype. PTL demonstrates a distinct preference for extranodal involvement; it mainly invades the contralateral testis and also the CNS and spreads aggressively, generally associated with high rates of morbidity and mortality, with the most common presenting symptom being painless unilateral testicular enlargement [9]. Some of the Systemic B symptoms are found in both patients of Hodgkin's and NHL, such as night sweats, fever, and weight loss (more than 10% within 6 months) and can be found in about 25–41% of 4–6 patients with advanced stage [10].

Orchiectomy is usually preferred as the primary treatment since it removes the malignant tumor, which is also helpful for further histopathological examination. Chemotherapy before surgery is usually not preferred due to the presence of a testicular blood barrier, and due to the presence of this barrier, it is difficult for chemotherapy drugs to reach the testes; at the same time, testicular tumor cells express drug-resistant proteins. Treatment showed reidentification of cancer cells at 2 years after orchiectomy surgery alone, even in patients with stage I [11]. Then orchiectomy followed by R-CHOP chemotherapy, IT injection of MTX, and radiotherapy to contralateral testis and lymph nodes could be considered. A study done by the International Extranodal Lymphoma Study Group-10 concluded that the collective risk of contralateral testicular relapse was 15% at 3 years and 42% at 15 years in patients treated without prophylactic testicular irradiation. In fact, prophylactic contralateral testis irradiation was effective in reducing the testicular relapse rate from 35 to 8% [5].

CONCLUSION

PTL is an uncommon condition for which a multidisciplinary treatment approach is required, which consists of orchiectomy, four to six cycles of anthracycline-based combination chemotherapy

with rituximab, contralateral testis irradiation, lymph nodes irradiation, and CNS prophylaxis.

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