

## Case Report

# Rare, rapid and resolved: a case of primary aggressive testicular non-Hodgkin's lymphoma

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### ABSTRACT

Primary testicular lymphoma (PTL) is a rare and aggressive extra nodal manifestation of non-Hodgkin's lymphoma (NHL), accounting for 1-2% of all NHL cases and 5% of testicular tumors. We report a case of a 62-year-old male presenting with a rapidly enlarging painless right testicular mass and right inguinal lymphadenopathy. Imaging and PET-CT revealed a metabolically active testicular mass with regional lymph node involvement. He underwent right high inguinal orchidectomy with inguinal lymph node excision. Histopathology and immunohistochemistry confirmed diffuse large B-cell lymphoma (DLBCL), non-germinal center type, double expressor phenotype. The patient received systemic R-CHOP chemotherapy with CNS prophylaxis and adjuvant radiotherapy. Follow-up PET-CT at 1 year showed complete remission. This case highlights the importance of a multimodal approach including surgery, immunochemotherapy, CNS prophylaxis, and scrotal irradiation for optimal disease control in PTL.

**Keywords:** Primary testicular lymphoma, Non-Hodkin's lymphoma, Diffuse large B-cell lymphoma, CNS prophylaxis, Multimodal treatment

### INTRODUCTION

Testicular lymphoma is a rare extra nodal manifestation of NHL representing 1 to 2% cases. It accounts for 5% of all testicular tumors.<sup>1</sup> The prevailing histological subtype is DLBCL, accounting for approximately 80% to 90% of adult testicular lymphoma cases.<sup>2</sup> On contrary, majority of testicular lymphomas in children consist of secondary involvement by Burkitt's lymphoma, DLBCL or lymphoblastic lymphoma. DLBCLs may be divided into three prognostically distinct subtypes GCB-DLBCLs, activated B-cell-like DLBCLs and type 3.<sup>3</sup>

These tumors commonly present after 60 years of age as a testicular swelling which is most commonly unilateral and painless. Synchronous bilateral testis involvement may be there in 10% of cases of PTL.<sup>4</sup> It may occur in isolation or in association with other neoplasms or immunodeficiency states such as immunosuppressive therapy, HIV infection, or tuberculosis.<sup>2</sup>

HIV infection being one of the most common risk factors for aggressive NHL.

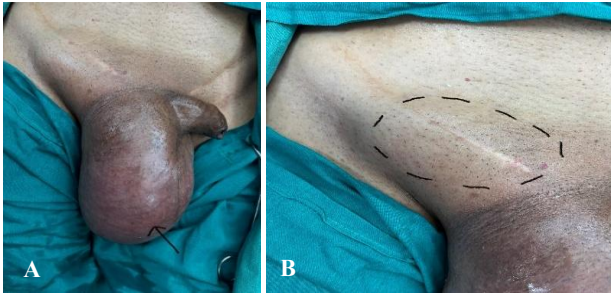
The majority of PTL patients (70-80% of cases) present in stage I or stage II but advanced stage cases with extra-nodal sites involvement of CNS, Waldeyer's ring, liver, bone marrow, lungs, pleura, adrenal, soft tissue or skin are also reported.<sup>4</sup> The incidence of CNS involvement has been reported in 44% of cases of PTL.<sup>4</sup>

A highly aggressive nature of the tumor, poor prognosis and high rate of recurrence makes its management challenging. The standard treatment approach for testicular lymphoma involves orchidectomy, followed by chemotherapy or radiotherapy.

Herein, we report a case of 62-year-old patient with primary testicular non-Hodgkin's lymphoma, that was successfully treated with surgery as well as the chemoradiation.

**CASE REPORT**

A 62-year-old male patient attended the OPD with chief complaints of painless mass on the right side of scrotum and right sided groin swelling for 2 months. Initially patient reported scrotal swelling first that was initially small and rapidly progressed to size of around 15 cm in a span of 2 months. Then the patient complaint of right sided groin swelling around 20 days after the scrotal swelling, that also was initially small and rapidly progressed to a size of around 8 cm in a span of 1 month.



**Figure 1: (A) Right sided testicular mass measuring approximately 15x8 cm; (B) right sided firm to hard, fixed, painless inguinal swelling measuring around 8x6 cm.**



**Figure 2: Right sided firm to hard, vascular testicular mass with gross hydrocele measuring approximately 16x10 cm with thickened spermatic cord and cremasteric hypertrophy.**



**Figure 3: Right inguinal conglomerated, hard, lymph node mass measuring approximately 7x6 cm in size.**

There was no history suggestive of cryptorchidism or any endocrine symptoms. There was no history of any fever, LUTS, bowel complaints, anorexia or cachexia or swelling elsewhere in the body. Patient is known hypertensive and diabetic well controlled on medications since the last 15 years. Past surgical history of bilateral hernioplasty was

present. General examination was normal. On physical examination, the abdomen was soft, non-tender. Local examination revealed a right sided testicular mass measuring approximately 15x8 cm that had variable consistency with absent testicular sensations. The left testicle was small, around 3 cm with soft consistency. Examination of the groin revealed a single right sided firm to hard, fixed, painless inguinal swelling measuring around 8x6 cm. Left groin normal. Bilateral hernioplasty scars seen.



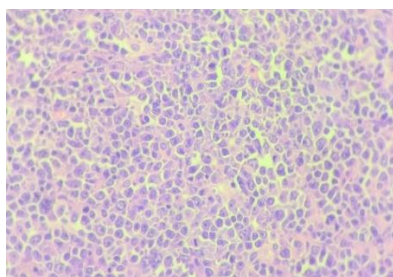
**Figure 4: Intraoperative image post excision.**



**Figure 5: Excised specimen-testicular mass (right) and conglomerated lymph node mass (left).**

Blood investigations, urinalysis, viral markers and tumor markers (Serum beta HCG, AFP) were within the normal ranges. Serum LDH was elevated-744 U/L (Normal 0-250 U/L). Further, radiological investigations were performed. Ultrasonography of whole abdomen, pelvis and scrotum revealed-Large 11.6x7.8x9.8 cm non homogenous mass with few septations and multiple small cystic areas- 466ccs in size with mild hydrocele noted. A large irregular cystic lesion with fluid and septations along right spermatic cord 6.6x3.8x3.8 cm-50 ccs in size. Contrast enhanced CT abdomen and pelvis showed-large heterogeneously enhancing solid mass lesion in the right scrotal sac measuring 12.8 (AP)x8.5(H)x7.9(W) cm with moderate septated hydrocele along with calcifications. A skip lesion seen at the root of right scrotum, anteroinferior to the right parasymphyseal region, measuring 4.8(H)x4.4(AP)x3.5(W) cm indenting the right crus. Enlarged heterogeneously right inguinal (5.2x3.6x3.1 cm), right external iliac (3.9x2.5x2.1 cm), precaval and right pelvic side wall (3.8x3.7x3.3 cm) seen with areas of necrosis. Rest abdominal structures appeared normal. No sclerotic or lytic osseous lesion present. Patient was then subjected to MRI scrotum that showed- enlarged right testis with heterogenous parenchyma measuring 12.5 cm in APx8 cm in transverse x8.9 cm in supero-inferior extent. Moderate hydrocele associated with the lesion. Right spermatic cord appeared thickened with

increased vascularity. Enlarged lymph nodes seen in the right inguinal region and base of scrotum. These showed areas of necrosis, and the largest lymph node measured 4.2×2.7 cm. Enlarged right obturator lymph nodes seen. Based on the above findings patient was then subjected to whole body FDG PET-CT scan that showed-metabolically active (SUV max-25.7) heterogeneously enhancing mass lesion with septations and areas of necrosis epicentered in the right testis, with right moderate hydrocele and thickened right spermatic cord measuring 12.4×8.6×9.3 cm. Metabolically active (SUV max 31.4) enhancing discrete and conglomerated retroperitoneal, right common iliac, right external and internal iliac, right inguinal and right obturator adenopathy approximately 6.5×5.2 cm in size. No metabolically active relevant disease seen elsewhere in the body.



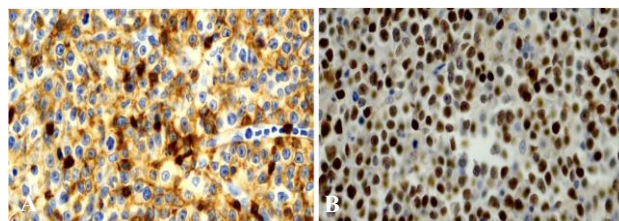
**Figure 6: HPE image - high-grade malignant tumor arranged in sheets.**

Individual tumor cells were large with vesicular nuclei and prominent nucleoli with brisk mitosis. Multiple foci of necrosis evident.

Based on the above findings, patient was worked up and then planned for surgery. Right sided high inguinal orchidectomy and excision of right sided inguinal lymph node mass done. Intraoperative findings revealed-right sided firm to hard, vascular Testicular mass with gross hydrocele measuring approximately 16×10 cm with thickened spermatic cord and cremasteric hypertrophy. Right inguinal conglomerated, hard, lymph node mass measuring approximately 7×6 cm in size. Post operative recovery was uneventful. Histopathology examination showed on macroscopy-right testicular mass lesion 16×10×6 cm with intact tunica albugenia. Cut section showed proliferative mass measuring 11×8×6 cm with multiple cystic areas. Right sided lymph node mass measuring 8×6×4 cm with whitish areas on cut section. On microscopic examination-multiple sections showing a high-grade malignant tumor arranged in sheets. Individual tumor cells were large with vesicular nuclei and prominent nucleoli with brisk mitosis. Multiple foci of necrosis evident. Spermatic cord margin was free of tumor. Section from the lymph node mass showed similar morphology. Testicular parenchyma did not visualise. Suspected diagnosis- NHL. Immunohistochemistry showed CD5 positive NHL of DLBCL non- germinal center type (Han's algorithm) with a double expressor phenotype (MYC+, BCL 2+). Cytogenetics and FISH showed- BCL6 translocation, high risk abnormality in DLBCL.

Patient was then referred to hemato-oncologist. After work-up and proper optimisation received 3 weekly, total 6 cycles of rituximab, prednisolone, oncovin, cyclophosphamide, hydroxydaunorubicin chemotherapy and 3 cycles of high dose methotrexate chemotherapy for CNS prophylaxis,

given with 14 days gap in between. Post chemotherapy course was uneventful. Post chemotherapy, PET-CT scan showed complete remission of all the nodal lesions and the surgical site lesion. He also received radiotherapy to the abdomen (Para-aortic and iliac regions) and contralateral testis to a dose of 45 Gy in 25 fractions by a direct anterior beam radiotherapy. Presently, he is asymptomatic and disease-free with no evidence of recurrent disease in the PET-CT scan in the last 1 year after the treatment.



**Figure 7: (A) IHC image showing CD5+, (B) BCL6+.**

## DISCUSSION

Primary testicular NHL (PTNHL) is a rare but highly aggressive malignancy, accounting for approximately 1-2% of all NHL and 5% of testicular tumors.<sup>5</sup> Unlike testicular germ cell neoplasms, PTNHL predominantly affects older men, with a median age at diagnosis of 60-70 years.<sup>6,7</sup> Patients most often present with a painless unilateral scrotal swelling; systemic “B” symptoms (fever, night sweats, weight loss) are uncommon at onset but may emerge with advanced disease.<sup>8</sup> Bilateral testicular involvement occurs in 6-10% of cases and is associated with a higher risk of relapse.<sup>9</sup>

Over 80% of PTNHL cases are DLBCL, non-germinal centre B-cell (non-GCB) subtype, characterized by large atypical lymphoid cells, frequent mitoses, and strong CD20 expression.<sup>6,7</sup> Immunohistochemistry typically reveals high Ki-67 proliferation indices (>70%) and expression of BCL-2 in a subset of cases.<sup>10</sup> Genomic profiling by Twa et al identified recurrent MYD88 L265P and CD79B mutations-hallmarks of activated B-cell (ABC)-type DLBCL-as well as alterations in immune-evasion genes (B2M, HLA class I), which may facilitate sanctuary-site relapse in the testis and CNS.<sup>12</sup>

The cornerstone of management is radical inguinal orchiectomy, both to secure diagnosis and to debulk disease.<sup>5</sup> Multimodal therapy-comprising orchiectomy followed by immunochemotherapy, CNS prophylaxis, and contralateral testicular irradiation-has markedly improved outcomes. In the pivotal phase II trial by Vitolo et al 5-year progression-free survival (PFS) and overall survival (OS) rates exceeded 70% with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), eight doses of intrathecal methotrexate, and 30 Gy scrotal radiotherapy.<sup>10</sup> Cheah et al further demonstrated that rituximab inclusion reduced systemic relapse by 30% and CNS relapse by over 50% compared with CHOP alone.<sup>7,9</sup>

Despite these advances, relapse remains a significant challenge. Zucca et al reported that, in the pre-rituximab era, CNS relapse occurred in up to 44% of cases, often within the first two years post-treatment.<sup>8</sup> Although rituximab and intrathecal prophylaxis have lowered this incidence to

approximately 10-15%, high-risk patients-particularly those with high international prognostic index  $\geq 3$ , elevated lactate dehydrogenase (LDH), or advanced stage continue to experience relapse in sanctuary sites.<sup>7,11</sup> PTNHL's predilection for the CNS and contralateral testis is thought to reflect the immune-privileged microenvironment, which may shield residual lymphoma cells from systemic immunosurveillance. Standard CNS prophylaxis includes intrathecal methotrexate; however, systemic high-dose methotrexate (3.5 g/m<sup>2</sup>) is under investigation to achieve better CNS penetration.<sup>13</sup> Similarly, prophylactic scrotal radiotherapy (25-30 Gy) to the uninvolved testis significantly reduces contralateral testicular relapse-from approximately 40% without RT to under 10% with RT.<sup>10</sup>

Prognosis in PTNHL is influenced by traditional DLBCL risk factors-age >60 years, elevated LDH, poor performance status, and extra-nodal involvement summarized by the IPI.<sup>11</sup> In Cheah et al international cohort (n=373), patients with low-risk IPI (0-1) achieved 5-year OS of 85%, whereas high-risk (IPI 3-5) had 5-year OS of 45% despite multimodal therapy.<sup>7</sup> Ren et al also found that incomplete chemotherapy cycles or omission of rituximab correlated with significantly inferior PFS and OS.<sup>11</sup> Given the unmet need in high-risk and relapsed PTNHL, several novel approaches are being explored. Small-molecule inhibitors targeting Bruton's tyrosine kinase (BTK), such as ibrutinib, have shown CNS activity and may complement immunochemotherapy in frontline or salvage settings.<sup>14</sup> Immune-checkpoint inhibitors (e.g., pembrolizumab) and chimeric antigen receptor (CAR) T-cell therapies represent promising strategies to overcome the immune-privilege barrier, though clinical data in PTNHL are currently limited.<sup>13</sup> High-dose chemotherapy with autologous stem-cell transplant (ASCT) has been employed in relapsed cases, demonstrating 2-year PFS rates of ~50% in small series, but prospective trials are needed to define optimal sequencing.<sup>13</sup> Finally, ongoing genomic analyses aim to stratify patients by molecular risk, guiding personalized therapy such as double-hit or double-expressor cases that may benefit from intensified regimens or targeted agents against BCL-2/MYC.<sup>12</sup>

## CONCLUSION

PTNHL, although rare and biologically aggressive can be effectively controlled through a multidisciplinary approach. Radical inguinal orchiectomy provides definitive diagnosis and local disease control, while systemic immune-chemotherapy (most commonly R-CHOP) addresses occult disseminated disease and significantly improves progression-free and overall survival. Given the high risk of central nervous system and contralateral testicular relapse, CNS prophylaxis (intrathecal and/or high-dose methotrexate) and contralateral scrotal radiotherapy are integral to the treatment paradigm. Long-term follow-up is essential due to potential for late relapse. Overall, the combination of surgery and chemotherapy augmented by prophylactic strategies represents the cornerstone of successful management in PTL.

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