Case Report

A Middle Aged Male with Granulomatous Orchitis: Primary Diffuse Large B-Cell Lymphoma of Testis Mimicking Tubercular Orchitis

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Abstract

Primary testicular lymphoma is a rarely seen testicular tumor accounting for 1-9% of all testicular tumors. It is a rare form of extra nodal non-Hodgkin's lymphoma representing 1% - 2% of non-Hodgkin's lymphoma. The dominant histological subtype is diffuse large B-cell lymphoma (DLBCL). It is the most common testicular malignancy in men aged over 60 years. Patients with primary testicular DLBCL show a continuously high risk of recurrence with no plateau in the survival curves and a tendency to involve other extra nodal sites, especially the central nervous system and the contralateral testis. Here we present a 60-year-old gentleman from Bangladesh presenting with fever and unilateral testicular mass for 3 months. Fine needle aspiration cytology (FNAC) from testicular mass revealed granulomatous orchitis and he was started anti tubercular medication without improvement. Later orchiectomy was done and Immunohistochemistry showed diffuse large B-cell lymphoma. He was referred to oncology for further management.

Keywords: Primary Testicular Lymphoma; Diffuse Large B-Cell Lymphoma; FNAC; Granulomatous Orchitis; Immunohistochemistry.

Introduction

Primary testicular lymphoma (PTL) was first reported by Curling in 1866.[1] It is a group of uncommon neoplasms, with the subtypes of diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and Burkitt's lymphoma.[2,3] In general, primary testicular DLBCL, the frequent subtype (80%-98%) among all, arises in old age (i.e., >60 years).[4,5,6] The typical clinical signs of testicular DLBCL include testicular swelling, B-symptoms and elevated lactate dehydrogenase (LDH) levels[7]. Bilateral instances account for around. 20% of all cases. In general, testicular DLBCL tumors are classified based on Cotswold modification of Ann Arbor staging system, where crucial disease parameters like tumor size, lymphadenopathy and regions of lymph node involvement are considered towards the assessment of overall clinical stage of the disease.[8] Primary testicular DLBCL has been reported to exhibit aggressive clinical behavior, poor prognosis and high tendency to disseminate to the central nervous system (CNS) and thereby related to high morbidity and mortality rates.[4,9] The hybrid 2-[fluorine-18] fluoro-2-deoxy-d-glucose (FDG) positron emission tomography/computed tomography (PET/CT) has become the standard imaging tool for initial staging and assessment of the treatment response in lymphoma patients.[10,11,12,13] There is no standard treatment modality for primary testicular lymphomas due to their rare occurrence, however, today, systemic chemotherapy(R-CHOP) and radiotherapy (25 Gy), prophylactic intrathecal chemotherapy are performed after orchiectomy. When considering all stages, 5-year survival rate is 12% for these tumors showing frequent relapses.[14]

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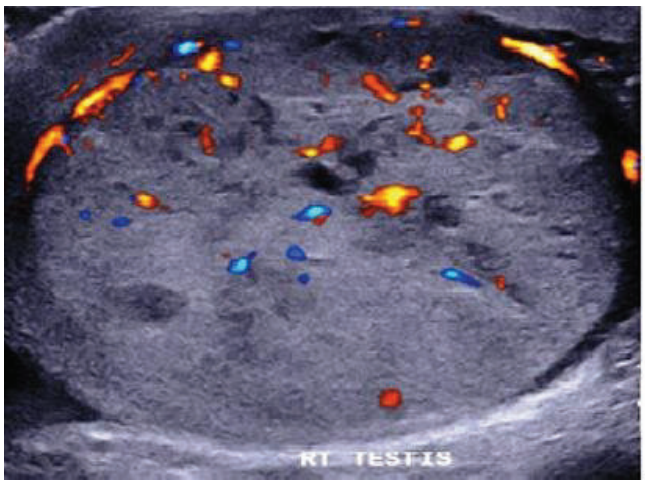
Case report

A 60 years old Bangladeshi gentleman presented to Urology department with symptoms of a lumpy and heavy right testicle without any tenderness. Both testes were initially the same size, however the patient noticed an increase in the size of this right testicle during the previous three months. The patient is a school teacher who had history of prolonged sitting, where the patient felt that the discomfort is getting worse while on the job. The patient denied previous complaints of testicular enlargement in himself and his parents, as well as history



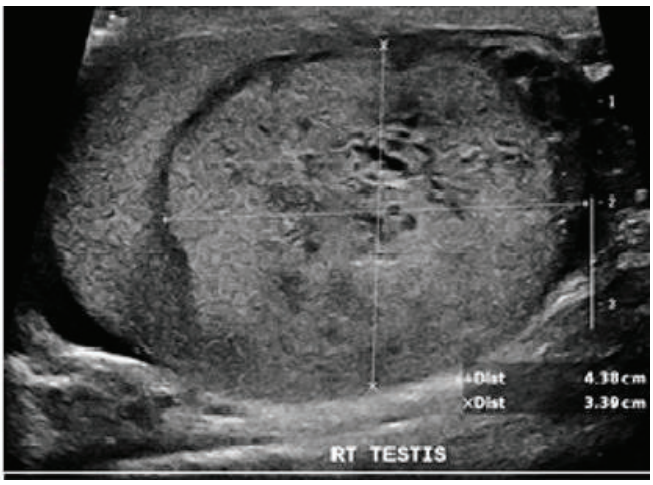


Figure 1 and Figure 2: Color Doppler ultrasonography of right Testis showed hypoechoic mass in the right testis with internal vascularization.

of undescended testicles, and previous surgery. Complaints related to malignancy include low back pain, cough and shortness of breath, decreased appetite (anorexia), nausea and vomiting, bone pain, weight loss, and weakness (malaise) which the patient denied. He also gave history of low-grade, intermittent fever, highest being recorded as 101°F with night sweat. On query, he stated that he had lost about 6 kg of his previous weight unintentionally. He had strong family history of tuberculosis. On physical examination, he was mildly anemic. No lymphadenopathy was present. On urological examination, a mass measuring 2 cm in diameter was palpable in his right testis, and the contralateral testis and other structures were found to be normal. Before being referred to our clinic, he was treated with various antibiotics, considering it to be chronic orchitis. The values were calculated as Hgb: 9.1 g/dL, Hct: 28.2%, WBC: 6.81 mm^3. There were no other abnormalities in the laboratory tests such as liver function tests, renal function tests, urine analysis, coagulation parameters, Mantoux test and tumor markers such as alpha-fetoprotein, beta-hCG. Also, serum antibodies against HIV were negative. Chest X-ray and abdominal ultrasound failed to reveal any mediastinal or intrabdominal lymphadenopathy respectively. Doppler ultrasonography of testis showed a hypoechoic mass, measuring about 21×17 mm in the right testis with internal vascularization. (Figure 1 and 2) There is also another hypoechoic mass, measuring about 24× 14 mm with internal vascularization in the tail region of right epididymis. Left testis and epididymis were normal.

FNAC from right testicular mass and histopathology was done, which showed effacement of testicular tissue with infiltration of small lymphocyte and histiocyte with scattered epithelioid cells suggestive of chronic granulomatous orchitis. (Figure 3).

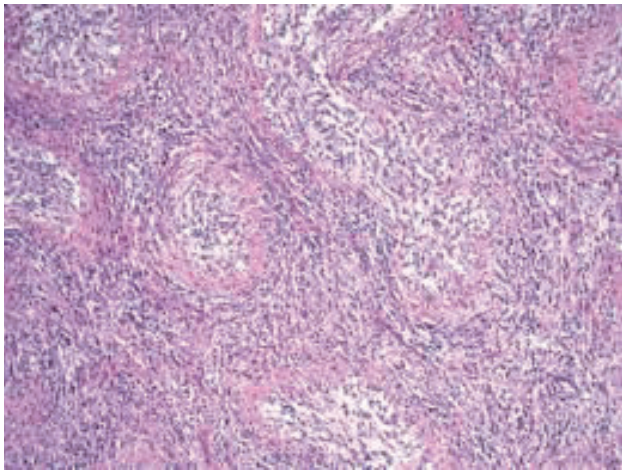


Figure 3: Testicular tissue showing scattered granuloma suggestive of chronic granulomatous orchitis

On the basis of history, positive family history and histopathology report, the patient was started anti tubercular chemotherapy according to weight and advised to follow up after 1 month. 2 weeks after starting treatment he again presented with high fever. Reevaluation revealed new development of right inguinal, firm, non-tender mobile lymphadenopathy. LDH was high (970U/L, normal below 250 U/L). Right radical inguinal orchiectomy was done. Immunohistochemical staining revealed positivity for

LCA, Ki 67(nuclear proliferation marker-80% positive), MUM1(Multiple myeloma oncogene), BCL 6(nuclear marker for germinal center B lymphocyte) & Pan B (CD20) and negativity for S-100, SMA, CD3(membrane marker for B lymphocyte), CD10. According to the World Health organization diagnosis criteria and using Hans algorithm, the diagnosis was DLBCL of testis with non-germinal center phenotype (Figure 4).

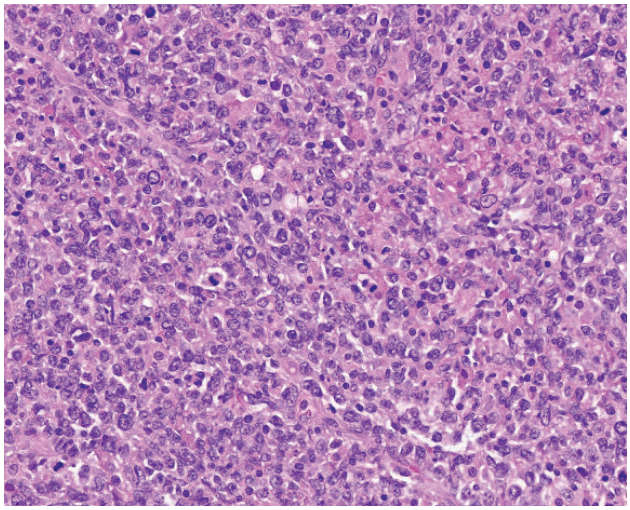


Figure 4: Immunohistochemistry of testicular tissue showing features of DLBCL, non-germinal center type.

According to the internal prognostic index (IPI), patients' IPI score was evaluated as 5 and according to Ann Arbor staging, patients' stage was interpreted as grade 3E. The patient was referred to the medical oncology and radiation department after the orchiectomy with the purpose of adjuvant chemotherapy and radiotherapy.

Discussion

PTL is a rare pathology that represents 1% - 2% of all malignant non-Hodgkin's lymphomas, 4% of all extra nodal malignant non-Hodgkin's lymphomas and 5%- 9% of malignant testicular tumors.[15,16,17] Age at diagnosis vary between 60 and 70 years.[18] Most cases are classified as a non-germinal center cell-of-origin subtype, which may partially account for the aggressive nature of the disease.[19]

The etiological and predisposing factors of the PTLs are not well understood. However, no relation between lymphoma and trauma, chronic orchitis, filariasis of spermatic cord or undescended testis was found.[20] Although specific risk factors for PTL are limited, HIV infection has been identified as a factor for aggressive NHL.[21] In HIV-infected patients, lymphoma occurs more extensively in extra nodal sites such as testis. Classification of primary testicular lymphoma that was modified by the Nordic Lymphoma Group is as follows: stage I: unilateral testis involvement with or without epididymis or cord involvement; stage II: abdominal and pelvic lymph node involvement; and stage II-IV: distant metastasis.

The usual symptomatology is a progressive increase in testicular volume over several months without pain [15,16]. It may be accompanied by fever, weight loss, or night sweats.[22] The presence of these systemic signs is predictive of tumor aggressiveness and is observed in 25% to 41% of patients with advanced disease.[16,23] Granulomatous orchitis, pseudolymphoma, plasmacytoma, and rhabdomyosarcoma are other conditions mimicking testicular lymphoma. The symptomatology was similar in our patient but general signs were absent.

The most important factors identifying prognosis are the clinical stage and histological grade.[24] It has been reported that a primary tumor larger than 9 cm, epididymis, presence of spermatic cord and bilateral testis involvement, vascular invasion, advanced age, high LDH levels, presence of B symptoms, high International Prognostic Index (IPI) score, and left testis involvement are factors associated with poor prognosis.[25] Nevertheless, young age, localized tumor, presence of sclerosis, small size of the tumor, low histologic grade and no epididymis or spermatic cord involvement are indicators of good prognosis.[26]

The classic physical sign in the localized stage is a solid testicular mass of variable size. This mass can be unilateral or bilateral. Bilateral localization is the most frequent according to the literature. It is synchronous in 10% and asynchronous in 30% - 35%. Our patient had a unilateral lesion.

Scrotal ultrasonography is the first-line examination for an enlarged scrotum.[16,27] It is often coupled with Doppler. It allows the mass to be highlighted with its measurements. In ultrasonographic examination, hypoplasia, diffuse enlargement, and increased echogenicity of the testis and loss of hypervascularity, or a striped pattern of the entire testis might be observed in neoplastic infiltrative diseases such as plasmacytoma, leukemia and lymphoma.[27] However, these features can be observed in inflammatory diseases such as chronic granulomatous orchitis and other inflammatory processes as well. Thus, in the absence of clinical signs and symptoms of inflammation, correct interpretation of

the findings might be challenging. Lactate dehydrogenase (LDH) levels are elevated, while BHCG and AFP are rarely elevated.[28] BHCG and AFP markers were normal in our patient.

Orchidectomy is essential because it is of diagnostic and therapeutic interest.[17,22,29,30] It is performed through an inguinal approach. It removes the so-called sanctuary site.[15,17] In the presence of the blood-testicular barrier, the drugs penetrate the testicles with difficulty and the effect of chemotherapy is not ideal [31]. At the same time, testicular tumor cells may also express high levels of drug-resistant proteins, such as P-glycoprotein (PGP) and breast cancer drug-resistant protein (BCRP), resulting in resistance to chemotherapy.[32]

The most common histologic subtype is diffuse large B-cell lymphoma, accounting for approximately 80 - 90% of testicular lymphomas.[17,22,29,33] On immunochemistry, tumor cells usually express pan-B-cell markers such as CD19, CD20, CD22, CD79a and PAX5. Surface and cytoplasmic immunoglobulins (Ig), most commonly IgM, are demonstrated in the majority of cases, and the Ki-67 proliferation index is high.[33]

Lumbar puncture for tumor cells in the CSF is recommended because the central nervous system is a preferred metastatic site.[34] Brain MRI is recommended in some studies.[22,35] Other metastatic sites include skin, lung, contralateral testis, Waldeyer's ring.[17,22]

For a long time, bone marrow biopsy and thoracic-abdominal-pelvic CT scans were used to differentiate between localized and metastatic disease.[5] Whole body 18-fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG- PET-CT) has a prominent place in the initial workup of lymphoma. It is more sensitive for the detection of other extra-ganglionic lesions.[35,36]

The Ann-Arbor classification is the staging system for primary testicular lymphomas. The vast majority (70% - 80%) are diagnosed at a localized stage (stage I - II).[16,37,38] Advanced stages (stage III - IV) are very rare.[33,34]

Due to the low incidence of the disease, no randomized phase III trials have been conducted and the therapeutic approach is based on data from phase II trials and retrospective studies.[36] A multimodal therapeutic approach is needed. The multidisciplinary team includes urologists, hematologists and radiation oncologists.[39] Orchiectomy is the preferred treatment since it removes the malignant tumor while also providing a biopsy sample for further histopathological examination. Chemotherapy before surgery is not optimal due to the presence of a blood-testicular barrier, which makes it difficult for the medicine to reach the testes, at the same time testicular tumor cells express drug-resistant proteins R-CHOP chemotherapy followed by central nervous system chemoprophylaxis and scrotal radiotherapy is the standard treatment for localized stage I–II PTL.[17,23,40] The addition of CNS prophylaxis with IV administered CNS-penetrating chemotherapy such as high dose methotrexate (HD-MTX) or high Dose cytarabine (HD-Ara-C) and/or IT chemotherapy as well as irradiation or excision of the contralateral testis are highly recommended.[23] In stage III-IV diseases, systemic chemotherapy, scrotal radiotherapy, and intrathecal chemotherapy are performed.

Conclusion

In conclusion, Testicular lymphoma is a rarely encountered, aggressive extra nodal non-Hodgkin's lymphoma which should be considered for every patient who is admitted with a testicular mass, especially if they happen to be in advanced age. Misinterpretation of the clinical findings as orchitis could delay the definitive diagnosis. Primary testicular lymphoma is a disease with a poor prognosis. The rare incidence of the disease, its development and tumor behavior being different from the germ-cell cancers of the should be kept in mind for patients who present with a mass in the testis, and the urologist, pathologist, and oncologist should take joint action.

Conflict of interest: None declared

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