


An Isolated Testicular Relapse of Burkitt's Lymphoma

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Introduction

Burkitt's lymphoma (BL) is a highly aggressive B-cell non-Hodgkin's lymphoma (NHL). Sporadic BL is observed in North America, Europe, and East Asia. While the most common presenting site of sporadic BL is the abdominal region, testicular involvement is observed in only about 6% of cases. Primary testicular BL often presents with other anatomical sites involved on further workup, indicating a heavy cancer burden. Although treatment for testicular relapse of BL is not well established, relapse chemotherapy regimens are typically used. Radical orchiectomy is justified for cases in which the testicle has been completely replaced by tumor. We present a unique case of a 7-year-old patient presenting with an isolated testicular relapse of BL, an occurrence that has not been reported in the literature to the best of our knowledge. Furthermore, it is also noteworthy that this isolated relapse occurred within only 6 weeks of a negative positron emission tomography/computed tomography (PET/CT) scan.

Case Presentation

A 7-year old Caucasian male with previously diagnosed BL status post standard chemotherapy with complete response presented to the emergency room for a 1-week history of right scrotal swelling. At the time of initial presentation, the patient was diagnosed with BL after his mother noted increased abdominal girth. An initial CT scan revealed pleural effusion, pericardial effusion, and small bowel wall thickening. Cytogenetic studies confirmed the diagnosis of BL with t(8;14) chromosome translocation seen on fluorescence in situ hybridization. Staging was high-risk group B, Stage III. The patient completed standard chemotherapy: COPADM (fractionated cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate), followed by rituximab and COPADM.¹ The patient tolerated the chemotherapy, and a complete response was observed

on the subsequent CT. A PET/CT scan performed 1 month prior to the most recent emergency room admission showed no signs of recurrence.

On presentation at recurrence, the patient had stable vital signs. Physical examination was remarkable for an enlarged and firm right scrotal mass that was non-tender to palpation (Figure 1). Cremasteric reflex was present bilaterally. Laboratory evaluation revealed normal complete blood count, serum creatinine, and serum electrolyte levels. Tumor markers, including serum β -human chorionic gonadotropin, lactate dehydrogenase, and α -fetoprotein were within normal limits. Scrotal ultrasonography revealed a diffusely enlarged, hyperemic, and heterogeneous right testis with a hypochoic mass-like lesion measuring $21 \times 10 \times 25$ mm (Figure 2, left). The right testis measured $4.0 \times 2.1 \times 3.2$ cm, while the left testis was $1.8 \times 0.6 \times 1.1$ cm.

Repeat CT of the chest, abdomen, and pelvis with contrast demonstrated no recurrence apart from a partially visualized right testicular mass (Figure 2, right). Given the negative tumor markers, the likelihood of testicular germ cell tumor was deemed low. A decision was made to perform a right trans-scrotal biopsy to obtain a tissue diagnosis. Intraoperatively, the right testicle was found to be completely replaced by tumor, with extension into the gubernaculum and epididymis (Figure 3). Intraoperative frozen section analysis was consistent with malignant neoplasm of the blood cell. Due to the significant tumor burden and low likelihood of testicular viability, a right orchiectomy was performed after an intraoperative consultation with a pediatric hematology-oncologist.

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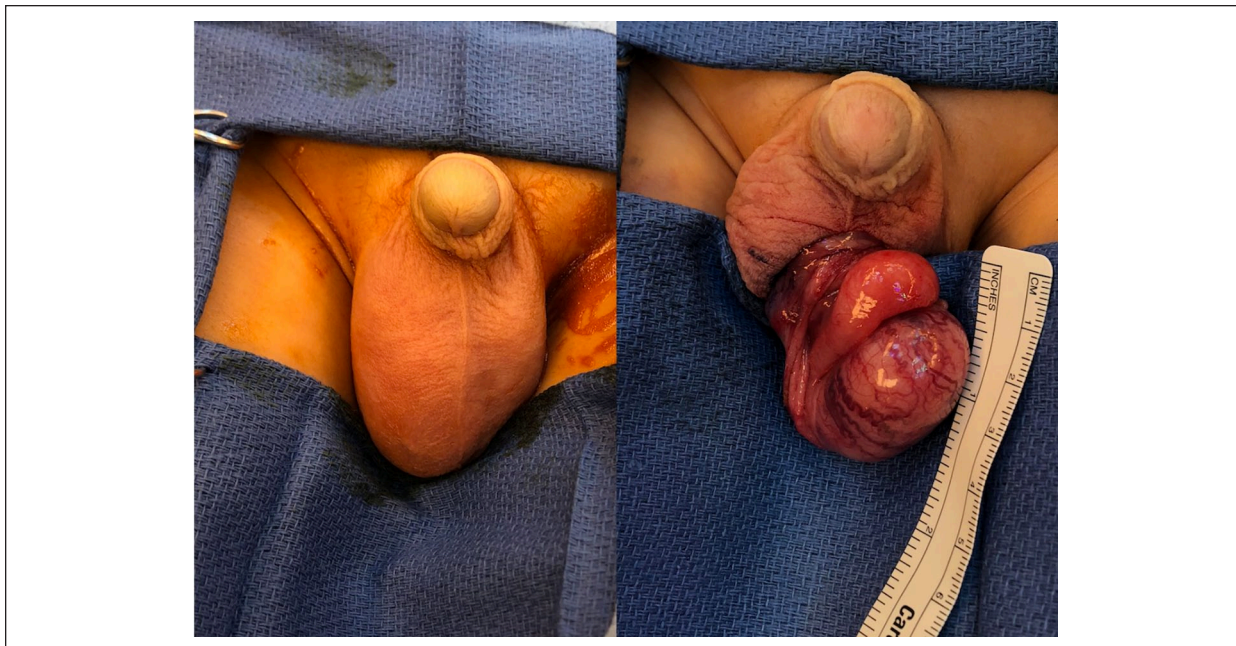


Figure 1. Intraoperative figure showing enlarged right scrotal mass (left). Tumor mass encompassing entire right testicle extending to the gubernaculum and epididymis (right).

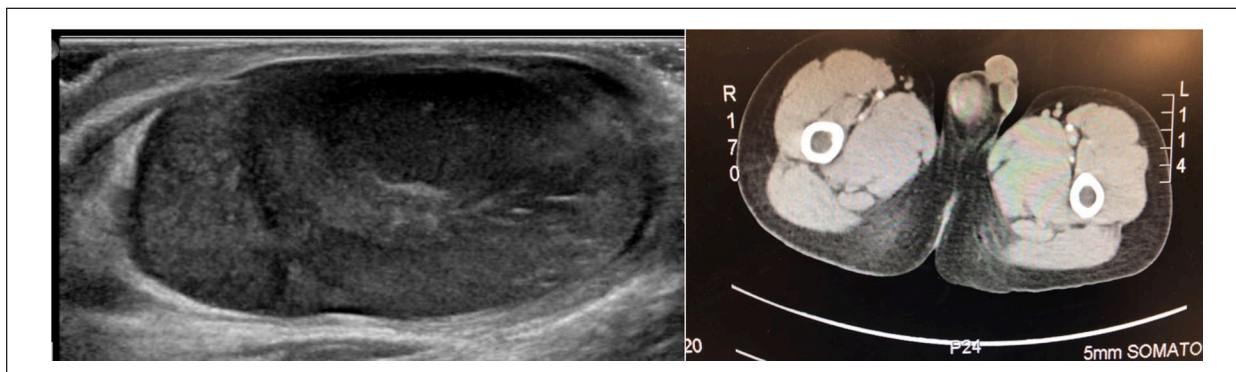


Figure 2. Scrotal ultrasonography of right testis depicting hypoechoic right testicular mass (left). Axial computed tomography scan of abdomen/pelvis depicting enlarged right testicular mass (right).

Gross pathologic, microscopic, and immunohistochemical examination can be seen in Figure 3. Immunohistochemistry showed the atypical cells were positive for CD20, PAX-5, CD10, BCL6, and c-MYC and variably positive for BCL2, but negative for CD3 (Figure 3). Fluorescence in situ hybridization indicated the presence of an abnormal fusion between MYC and immunoglobulin H probes corresponding to 8;14 translocation. This, in conjunction with a negative subsequent bilateral bone marrow aspirate and biopsy, confirmed an isolated right testicular relapse of BL.

Postoperatively, the patient has completed 2 cycles of R-ICE therapy (rituximab, ifosfamide, carboplatin, and

etoposide) to date, and is awaiting autologous bone marrow transplant scheduled for early 2019.² He is tolerating the chemotherapy regimen well, while receiving Neupogen (filgrastim) for neutropenia with no signs of recurrence on 1-month follow-up.

Discussion

Burkitt's lymphoma is a highly aggressive B-cell NHL, with a doubling time of 24 hours.³ While the endemic type of BL is usually seen in the African subcontinent and is more commonly associated with Epstein-Barr virus and malaria, sporadic BL is observed in North

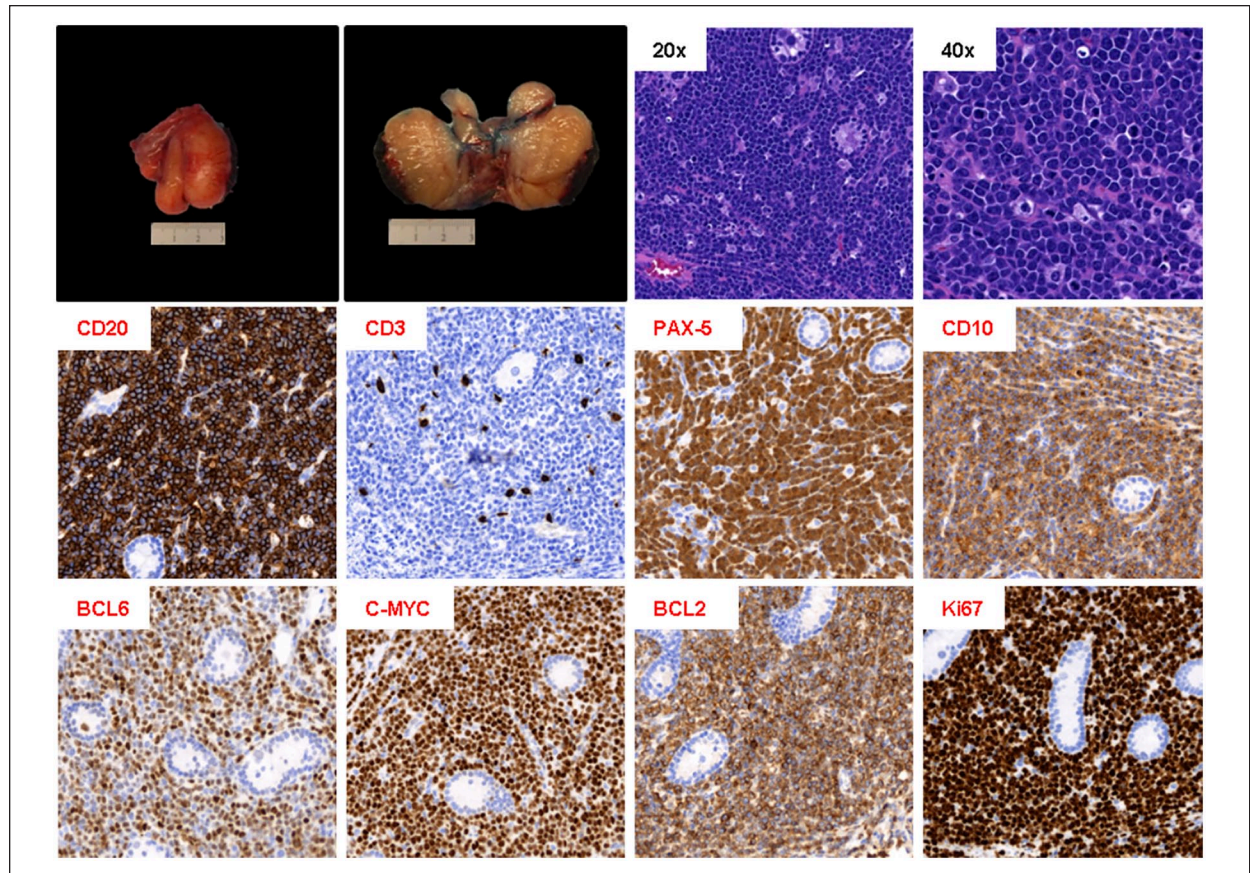


Figure 3. First row: Testis with attached spermatic cord and epididymis (first from left). Cut surface shows complete replacement of the testis, epididymis, and spermatic cord with firm white-tan fleshy tumor (second from left). At 20 \times , a “starry sky” appearance is present with a diffuse infiltrate of monotonous medium-sized atypical lymphoid cells with scattered tingible body macrophages (third from left). At 40 \times , atypical lymphocytes show oval to irregular nuclei with finely clumped chromatin, prominent paracentrally located nucleoli, and scant basophilic cytoplasm (first from right). Second and third rows: Immunohistochemistry stains are shown.

America, Europe, and East Asia with an annual incidence of 2 per 1 million.⁴ The most common presenting site of sporadic BL is the abdominal region (60% to 80%), followed by the head and neck area. Rarer sites of presentation include the mediastinum, central nervous system, skin, breast, thyroid, and testis.⁴ Testicular involvement is observed in about 6% of sporadic BL.⁵ Primary testicular BL often presents with other anatomical sites involved on further workup, indicating a heavy cancer burden. Leonard et al reported a case of a 10-year-old boy who initially presented with right testicular swelling, but with liver metastasis and right pleural effusion on further staging workup.⁶ Another report details the case of a 9-year-old boy who initially presented with dysphagia and left scrotal swelling, but further radiologic workup demonstrated an additional paravertebral soft tissue mass extending from T7 to L1.⁷

The mechanism behind testicular relapse of BL is not entirely known, but a lower temperature in the scrotum and the presence of the blood-testis barrier may reduce the therapeutic efficacy of chemotherapy. Hence, this may increase potential for testicular relapse.⁸ Kellie et al noted testicular relapse on follow-up in 3 cases (7%) in their review of 131 children with NHL at the St. Jude Research Hospital.⁹ Two of these patients had diffuse undifferentiated, non-BL, and the histology of the third case is unknown. Thus, an isolated testicular relapse of BL has not been reported in the literature to the best of our knowledge. Furthermore, it is also striking that this isolated relapse occurred within only 6 weeks of a negative PET/CT scan.

Surveillance physical examination should be performed periodically for prompt diagnosis of testicular relapse, and high clinical suspicion should be raised for patients with a previous diagnosis of NHL who present

with scrotal swelling. Scrotal ultrasonography is an excellent imaging modality to characterize the mass. PET/CT may be used to detect testicular relapse as well as aid in staging. It is also important to obtain serum tumor markers to rule out testicular germ cell tumors. While the prognosis of primary testicular lymphoma is poor, the major pathologies of such lymphomas in the literature have been limited to diffuse large B-cell lymphoma (BCL). Therefore, the specific prognosis of an isolated, unilateral testicular BL is, in fact, unknown. Previous studies have mentioned that older age, black race, and advanced stage are associated with a worse survival in patients with BL.¹⁰ Although BL is classically negative for BCL2 expression, cases with BCL2 staining have been described, as present in our case.^{11,12} BCL2 is known to be a MYC/BCL2 co-expresser, a feature associated with poorer outcome in diffuse large BCL, but this has not been correlated with worse survival outcome in BL.¹³

Although treatment for testicular relapse of BL is not well established, relapse chemotherapy regimens are typically used. While one reported case of synchronous bilateral testicular and left orbital involvement in a child with BL was successfully treated with chemotherapy alone, radical orchiectomy is justified for cases in which the testicle has been completely replaced by tumor, as present in our patient.¹⁴ Furthermore, this can be beneficial in tissue diagnosis and staging.¹⁴ Some reports support the use of radiation for both supplementary treatment to chemotherapy due to testis-blood barrier and as prophylaxis for possible central nervous system involvement.⁹ However, this should be weighed carefully against concern for future fertility impairment after radiotherapy in a young child. Collaborative efforts among pediatric urologists, pediatric hematology-oncologists, and primary pediatricians are of utmost importance to the care of patients such as ours in order to make judicious clinical decisions, maintain close surveillance, and offer appropriate counseling to the patient and their families on the types of treatments available and their potential side effects.

Author Contributions

YSK: Contributed to conception and design; drafted the manuscript; critically revised the manuscript.

FM: Contributed to conception and design; drafted the manuscript; critically revised the manuscript.

NRP: Contributed to conception and design.

VS: Contributed to acquisition, analysis, or interpretation.

NP: Contributed to acquisition, analysis, or interpretation.

RAD: Critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JGB: Critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethics approval was not needed.

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Informed Consent

Informed consent was obtained.

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