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Testicular relapse of acute lymphoblastic leukemia☆

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ABSTRACT

Contemporary chemotherapy regimens have led to improved survival and decreased incidence of testicular relapse for pediatric patients with acute lymphoblastic leukemia (ALL). Local therapies to the testes, such as radiotherapy and orchiectomy, are often not necessary given that high-dose chemotherapy agents can overcome the relative blood-testis barrier. However, urologists should be aware of clinical scenarios involving ALL which still warrant testicular biopsy to guide management. Here, we present a case of a 12-year-old boy with high-risk pre-B cell ALL presenting with a testicular relapse and a clinical presentation overlapping with non-infectious epididymo-orchitis.

1. Introduction

While modern chemotherapy regimens have made routine testicular biopsy for acute lymphoblastic leukemia (ALL) obsolete, there are several points during the management of ALL at which biopsy may be indicated to guide management.[1] One such indication is equivocal testicular involvement at the time of bone marrow or central nervous system relapse. Here, we present a case of ALL testicular relapse where clinical presentation, exam, and imaging findings overlapped with epididymo-orchitis.

2. Case presentation

A 12-year-old boy with no significant past medical or surgical history presented with weakness. He was found to have hyperleukocytosis with a white blood cell count (WBC) of 486 thousand/mm^3. He was diagnosed with high-risk pre-B cell acute lymphoblastic leukemia (ALL) with central nervous system involvement. There was no overt testicular involvement at the time of diagnosis. He underwent induction chemotherapy with vincristine, daunorubicin, prednisone, PEG-asparaginase, and intrathecal cytarabine and methotrexate, per the AALL1732 protocol. He had a good response, and he was continued on consolidation and maintenance chemotherapy per AALL1131.

While on maintenance therapy nine months after his leukemia diagnosis, the patient developed right testicular pain and swelling. He was afebrile and hemodynamically stable, with a WBC of 2.9 thousand/mm^3 and negative urinalysis. Urine culture grew 10–50,000 CFU/ml mixed urogenital flora. The right testicle was erythematous, tender, edematous, and soft on exam. Testicular ultrasound showed heterogeneous parenchyma, epididymal hypervascularity, a complex septated hydrocele and thickened scrotal skin, overall radiographically consistent with epididymo-orchitis with a reactive hydrocele (Fig. 1, A). No distinct mass was appreciated on exam or imaging. The patient had modest clinical improvement on ceftriaxone and was discharged on levofloxacin.

One week later, he re-presented to the oncology department with leukocytosis (WBC 16 thousand/mm^3). Peripheral flow cytometry confirmed early systemic relapse of B-ALL and chemotherapy was resumed. He then developed fever, tachycardia, hypotension and worsening testicular pain and swelling. Ultrasound suggested worsening epididymo-orchitis (Fig. 1, B). Urine culture grew 10–50,000 CFU/mL of multidrug-resistant Klebsiella pneumoniae. He was started on meropenem. His hemodynamics, fever curve, and testicular exam improved. Follow-up ultrasound showed improvement, but persistent abnormalities (Fig. 1, C). It was unclear whether the improvement was related to antibiotic or chemotherapy administration.

After multidisciplinary discussion between oncology and urology, it was decided to pursue testicular biopsy, due to clinical suspicion of testicular ALL recurrence, as well the implications for addition of radiation therapy to his systemic and intrathecal chemotherapy if a testicular relapse was confirmed. A surgical testicular biopsy was performed, with pathology revealing involvement of the parenchyma by B lymphoblastic leukemia (Fig. 2).

Testicular radiation was performed bilaterally (24 Gy, 12 fractions),

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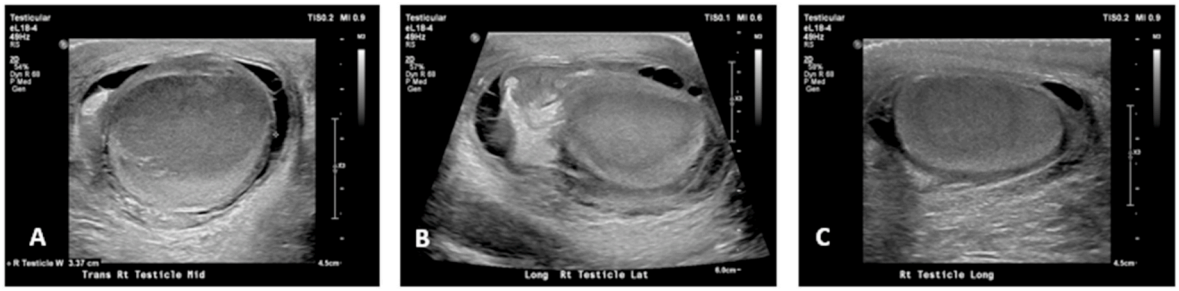

Fig. 1. (A) Presentation ultrasound (B) Second presentation ultrasound (C) Pre-biopsy ultrasound.

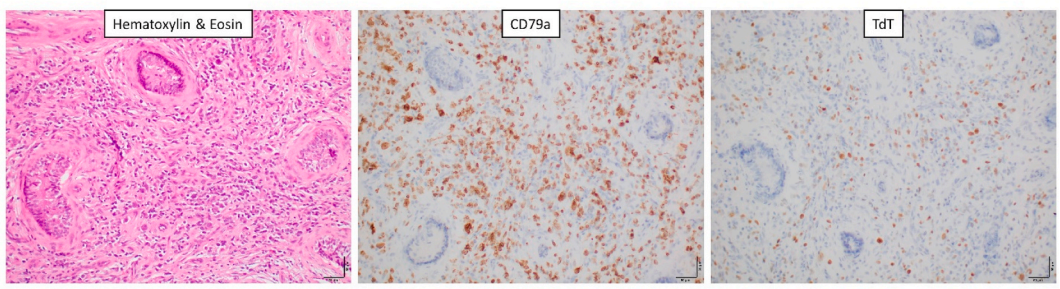

Fig. 2. Testicular biopsy showing involvement by B lymphoblastic leukemia. Photomicrographs at 200x original magnification.

which the patient tolerated well. He was continued on salvage chemotherapy with etoposide and cyclophosphamide and intrathecal VP-16/cyclophosphamide.

Three months later, after failing several systemic treatment regimens, the patient's disease unfortunately progressed to refractory, terminal mixed-phenotype acute leukemia. He ultimately died 14 months after diagnosis.

3. Discussion

The 5-year survival for pediatric ALL now exceeds 90%, but relapse rates remain around 15–20%.[1,2] Historically, the testes were regarded as pharmacologic sanctuary sites, with the blood-testis barrier preventing large-molecular weight chemotherapy agents from passing into the seminiferous tubules and interstitial spaces.[1,3] This barrier is now understood to be relative, and current high-intensity chemotherapy regimens for ALL achieve concentrations high enough to overcome it. Modern chemotherapy regimens—incorporating agents such as high-dose methotrexate, vincristine, asparaginase, and cyclophosphamide—have largely obviated the need for local therapies for testicular involvement at the time of diagnosis. Testicular involvement has been demonstrated to be sensitive to chemotherapy.[4] Now, overt testicular involvement at the time of ALL diagnosis has no independent prognostic significance.[5]

Moreover, modern regimens have decreased the incidence of ALL testicular relapse from 6 to 12% in the 1970s to 0–2% since 2000.[1] Thus, routine testicular biopsy at the time of ALL diagnosis or after induction chemotherapy is no longer recommended. However, testicular biopsy remains prudent in several situations during the course of disease, including apparent isolated testicular involvement at the time of diagnosis or relapse; persistent enlargement or abnormal ultrasound imaging after induction therapy; and equivocal testicular involvement at the time of bone marrow or central nervous system relapse, as with our patient.[1] In each of these cases, identification of testicular involvement can alter management, such as the choice or intensity of chemotherapy regimens or the addition of testicular radiotherapy or orchiectomy.[1,2] When testicular relapse is suspected, biopsy should be pursued expediently, as chemotherapy effects may lead to a false negative biopsy.

It is also important to note that any local testicular therapies should be administered as adjuncts to systemic treatment. Clinically-isolated testicular leukemia is treated as systemic disease, given that systemic relapse occurs within months of testicular radiation or orchiectomy administered alone.[1]

In determining specific treatment regimens for relapses involving the testes, the timing of the relapse (early, $<$18 months after diagnosis; intermediate, 18–36 months after diagnosis; or late, $\geq$36 months after diagnosis) and sites of the relapse (bone marrow, central nervous system, and/or testes) are guiding factors. Depending on these factors, consideration can be given to local therapies including testicular radiotherapy (alone or as a boost with total body irradiation) and orchiectomy with or without prophylactic radiation to the contralateral testis.[1] Thus, both the decision for testicular biopsy and decisions on subsequent management should be made by a multidisciplinary team.

4. Conclusion

Testicular relapse may not present with a distinct mass on imaging or exam and clinical findings can overlap with infectious or noninfectious epididymo-orchitis. A high index of suspicion for testicular relapse must be maintained in leukemic patients, as identification of relapse can alter management. A missed opportunity to treat testicular relapse can have devastating implications for prognosis. Thus, urologists should be aware of clinical scenarios involving ALL which warrant testicular biopsy to guide management.

Consent

Consent was deemed not applicable for this retrospective case review by the institutional internal review board.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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