Incidence and detection of testicular leukemia in children[1]

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The current treatment of acute lymphocytic leukemia in children continues to result in improved survival statistics. Unfortunately, some children who appear to be free of disease show a relapse because of an apparent propensity of leukemic cells to infiltrate the testis and resist conventional therapy. In an effort to detect subclinical testicular leukemia, 14 males with acute lymphocytic leukemia achieving 36 months of continuous complete remission due to protocol chemotherapy underwent routine bilateral testis biopsy immediately prior to the planned cessation of maintenance chemotherapy. Biopsy findings determined the need for testicular irradiation and reinduction of systemic chemotherapy. Thirteen patients had palpably normal testes at the time of biopsy and no histologic evidence of leukemic testicular infiltration. One patient had a normal right testis and a firm left testis with bilateral leukemic involvement as shown by the biopsy results. This represents a 7.1% incidence of occult testicular leukemia. Theoretic considerations of leukemic infiltration of the testis and the improved prognosis of patients treated for residual or persistent testicular disease suggest the need for a reliable method to detect testicular leukemia. This experience with routine testicular biopsy of palpably normal testes and with biopsy of palpably abnormal testes with testicular infiltration in patients still undergoing chemotherapy suggests that physical examination alone is a reliable method to detect leukemic testicular infiltration in most patients. Nevertheless, continued routine biopsy immediately prior to cessation of maintenance chemotherapy is still recommended to ensure that patients with occult testicular leukemia are identified.

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Isolated testicular infiltration of acute lymphocytic leukemia (ALL) of childhood may occur in the absence of

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Table 1. Physical examination and testicular biopsy

13 patients	Palpably normal testes and negative bilateral biopsy
1 patient	Firm left, normal right testis and positive bilateral biopsy

sence of relapse at other sites.[1-3] Recurrence of the disease in the testis during maintenance chemotherapy usually indicates concomitant or subsequent bone marrow, central nervous system (CNS), or systemic relapse and therefore is associated with a poor prognosis.[1,3-6] Testicular leukemic infiltration after establishment of clinical remission and cessation of therapy, however, has been amenable to local irradiation and reinstitution of systemic chemotherapy, resulting in prolonged survival.[1,5,7,8] Because early reports indicated that patients may have occult, clinically silent testicular involvement,[5,9,10] we have followed a policy of bilateral testicular biopsy in all male patients who had ALL during childhood. Biopsy was performed immediately prior to cessation of therapy following three years of continuous complete remission in an effort to identify and treat as early as possible those patients with isolated testicular infiltration. We describe our experience with 14 such patients.

Materials and methods

Ninety male patients with a diagnosis of ALL were seen at The Cleveland Clinic Foundation from 1965 to 1979. All were treated with induction chemotherapy and CNS prophylaxis according to various standard regimens, most recently according to Pediatric Oncology Group protocols. After initial remission was obtained, standard maintenance chemotherapy was begun. Patients achieving 36 months of continuous complete remission underwent bilateral testis biopsy to determine the need for continued systemic chemotherapy and/or testicular irradiation. Therapy was discontinued if the results of the testis biopsy were negative for leukemic infiltration.

Fourteen of the 90 patients met the criteria for testis biopsy (i.e., 36 months of continuous complete remission) and, under general anesthesia, underwent a bilateral open biopsy; no complications resulted. One patient who achieved 36 months of continuous complete remission did not undergo biopsy and is excluded from analysis. (He remains alive with no evidence of disease and palpably normal testes 94 mo after diagnosis.)

Results

The 14 patients undergoing biopsy were between 4 and 22 years old. Thirteen patients with palpably normal testes at the time of biopsy had no histologic evidence of leukemic infiltration (*Table 1*). Biopsy results were positive for 1 patient who had a firm left testis, but a normal right testis. Thus, only a single instance (7.1%) of true occult testicular infiltration (palpably normal testes and positive biopsy findings) occurred. By comparison, the incidence of occult testicular involvement in several other series in which routine bilateral biopsy was performed after 24 to 36 months of continuous complete remission was 11.8% (range, 4% to 33%; *Table 2*).

Of the patients with negative biopsy results, 11 of 13 are alive and no longer undergoing therapy, with no evidence of disease 9 to 60 months after biopsy (mean, 28.6 mo). One patient is alive and undergoing treatment for a CNS relapse 23 months after biopsy. One patient died of bone marrow relapse 35 months after biopsy. He had had a negative biopsy result at the time therapy was stopped. Leukemic infiltration of both testes was demonstrated at autopsy. The only patient with a positive biopsy result received 2,600 rads of external beam irradiation to each testis, underwent reinduction systemic chemotherapy, and is alive with no evidence of disease, and is undergoing maintenance chemotherapy 23 months after biopsy.

Discussion

The occurrence of isolated testicular leukemic infiltration associated with ALL in patients otherwise free of disease has led to the postulate that the testis is a "sanctuary" where leukemic cells are protected from systemic chemotherapeutic agents.[9,11] Such protection has been ascribed to the anatomic impenetrability of the testis (i.e., the blood-testis barrier) or to the reduced cytotoxic activity in the cooler testicular environment.[3,9,12] When leukemic involvement of the testis is overt (painless enlargement and firm consistency to palpation[13]), the presence of disease is readily apparent and the need for further therapy is obvious. Yet, the occurrence of occult testicular leukemia (palpably normal testes with leukemic infiltration as shown by biopsy findings) in patients thought to be in remission raises the

question of whether a physical examination by itself is sufficient to detect testicular involvement. Some experience with patients undergoing maintenance therapy suggested that a physical examination alone might not be sufficient to detect testicular disease. Oakhill et al[5] found that 13 of 15 patients with a relapse of the disease in the testes had had normal examinations, but positive biopsy findings. Finkelstein et al[9] demonstrated bilateral leukemic infiltrates in 3 patients who presented with only unilateral testicular enlargement during remission. Other reports, however, have suggested that a careful preoperative physical examination will disclose a palpably abnormal testis when leukemia is present. Stoffel et al[3] reported 19 episodes (13 patients) of relapse in the testes; all patients had had abnormal testes examinations. In a larger series, Nesbit et al[4] found that all 20 patients with positive biopsy results had enlarged testes when relapse of ALL was suspected. Our own experience with patients with relapse while undergoing therapy also suggests that unsuspected infiltration is unusual. In 6 patients undergoing therapy with relapse in the testes, only one palpably normal testis was positive according to biopsy findings.

A physical examination to detect relapse at the end of maintenance therapy also appears adequate in most patients, with occult leukemia occurring in only 11.8% (*Table 2*). Our own data confirm this, with only a single discovery of unsuspected testicular involvement (*Table 1*). The detection of testicular leukemia by examination or biopsy at the end of maintenance therapy is important for patient survival. Nesbit et al[4] have shown that patients with relapse in the testes following cessation of maintenance therapy suffer from a relapse in the bone marrow less frequently and later than those with relapse in the testes while undergoing therapy. Furthermore, several authors have shown prolonged survival in patients with isolated relapse in the testes occurring after clinical remission and cessation of therapy when treated with reinduction chemotherapy and testicular irradiation.[1,5,7] In our series, one patient with residual testicular disease who is undergoing therapy has survived for 23 months.

Our data suggest that a careful physical examination is a reliable way of detecting testicular leukemia in most patients, but biopsy remains necessary to ensure that a significant proportion (11.8%) with treatable disease are not overlooked. Continued routine biopsy of all patients at the conclusion of maintenance therapy is therefore indicated until a better method of detecting testicular leukemia becomes available.

Table 2. Incidence of occult testicular leukemia (palpably normal testes with positive biopsy) in patients undergoing routine testicular biopsy after 24–36 months continuous complete remission

Author	Number with positive biopsy/Total number biopsied	%
Shepard et al[14]	1/25	4.0
Present study	1/14	7.1
Askin et al*[1]	5/59	8.5
Bowman et al[6]	7/70	10.0
Land et al[8]	5/49	10.2
Askin et al*[1]	9/65	13.9
Rosenkrantz et al[10]	2/6	33.3
Wong et al[15]	6/18	33.3
TOTAL	36/306	11.8

* Two sets of patients in different time spans.

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