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ISOLATED TESTICULAR RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Testes have been considered as a sanctuary site for leukemic cells in acute lymphoblastic leukemia. Isolated testicular relapses results in poor outcomes in boys as compared to girls. Testes are one of the most common extramedullary sites of relapse in acute lymphoblastic leukemia. With chemotherapy and or radiotherapy isolated testicular relapses are completely cured. The study was aimed to observe the incidence and outcome of isolated testicular relapse in leukemic child. Nine diagnosed children with acute lymphoblastic leukemia between 4-11 years were enrolled. Most of the child presented with anemia, bone pain and organomegaly. The children who developed testicular swelling had undergone testicular biopsy. All enrolled children had received chemotherapy (MRC 841 protocols) along with testicular irradiation and maintenance therapy. They underwent complete remission during induction and local field irradiation. One child had developed hepatitis with typhlitis and succumbed subsequently during maintenance therapy. Three children had bone marrow relapse during maintenance phase and expired at sixteen months of therapy. The remaining five children had completed maintenance therapy within the stipulated time of 24 months. One child had developed bone marrow relapse following six months of chemotherapy. The rest four children had second remission following completion of maintenance therapy with disease-free survival of 48 to 120 months. Evaluating endocrine and sexual function of the survived children who normally progressed to puberty. Testosterone replacement therapy was given in one child who developed normally. Ten years' event-free survival of the survived children with aggressive therapy was 43.5% without any significant adverse effects. So, chemotherapy and or radiotherapy in schedule dose and duration in an isolated testicular relapse in acute lymphoblastic leukemia has good outcome.

KEYWORDS: Acute lymphoblastic leukemia, Testicular relapse, Aggressive chemotherapy, Radiotherapy, Sanctuary site.

INTRODUCTION

Leukemia is defined as the malignant switch of hematopoietic precursor cells categorized into lymphoid and myeloid lineages based on the type of cell and acute or chronic condition of the disease.[1-2] The most common types of cancer based on the rate of incidence in children are acute lymphoblastic leukemia (ALL), central nervous system tumors, and lymphoma constituting half of the total malignancies. It is commonly seen in children but can be found at any age.[1,3] It comprises almost one-fourth of cancers in children from 0-15 years.[4] In Bangladesh, though the exact incidence is unknown, there appears to be an increase in the case of childhood malignancies. Yet, if we take cognizance of the incidence of other countries of this region, we can presume that 5 to 6 thousand new cases should be diagnosed each year.[5] Pediatric ALL is the most common and yet curable childhood malignancy within the pediatric cancers group of children.[6-7]

Testes in ALL children have long been considered to be a sanctuary site for the leukemic cells and testicular relapses are accountable for the major proportion of poor outcomes in boys compared to girls. Aggressive chemotherapy with intermediate or high dose methotrexate, testicular relapses are decreased from 0 to 2.8%.[8-10] ALL in boys, testes are the most common site of relapse with a reported incidence of 7% to 33%.[11-15] The incidence of isolated testicular relapse (ITR) varies from 3% to 16% of children during chemotherapy and 7% to 40% during off therapy.[11,13-14,16] Front-line therapies in these children have reduced these intensities.[9,17] Testes are the second most common site of extramedullary relapse in boys in ALL.[18] The children with ALL who had apparent ITR (painless

enlargement of testicle with diffuse leukemic cell infiltrations) during or after completion of initial chemotherapy are found with subsequent bone marrow relapse and death.[13,19-21] The chance of survival is poor when a patient relapses on chemotherapy.[19,21] The children with ALL and microscopic testicular leukemia are identified by routine biopsy at the end of continuation therapy had found good prognosis after re-treatment.[12-13,15] Without intermediate-dose methotrexate testicular relapses have significantly reduced to 3.2%.[22] We had performed testicular biopsy in children where there was minimum suspicion of testicular involvement.

There is little information in the literature review describing the outcome of a large series of patients with ITR when treated intensively and uniformly. Now, the focus has been shifted to the pathogenesis of ITR and its impact on survival as compared to relapse at other sites. As the boys survive in the second remission following salvage chemotherapy, long term consequences of treatment on puberty and sexual function are likely to become more important.

MATERIALS AND METHOD

This study was carried out in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Bangladesh from January 2005 to December 2010 on nine diagnosed ALL children from 4-11 years who had an isolated testicular relapse. The children who had previous or concurrent bone marrow relapse or any sorts of chemotherapy or radiotherapy were excluded from the study. The diagnosis was made on complete blood count and peripheral blood film, serum lactate dehydrogenase, bone marrow aspiration, testicular biopsy, and immunophenotype. The patient was evaluated who fulfilled the inclusion and exclusion criteria. The children had received MRC 841 protocol which includes 4 weeks with vincristine 1.5 mg/m^2 iv on day 1,8,15,22; daunorubicin 60 mg/m^2 iv on day 2 and 3; Inj. L-asperaginase 6000 IU/m^2 deep im in every alternate day from third day of induction to a total of 9 doses; tab. prednisolone 40mg/m^2 orally from first day in each week of vincristine therapy; IT methotrexate12.5mg on day 1,8,15,22; central nervous system (CNS) directed therapy with high dose methotrexate (5gm/m^2iv); repeated induction is given with same dose of drug given in induction phase. Consolidation phase was given with Inj. vincristine, IT methotrexate, inj. cytosine arabinoside, and inj. daunorubicin. The maintenance phase was continued up to three years with monthly vincristine, oral prednisolone, or etoposide for first five days, IT methotrexate was given monthly for initial three months, then three monthly for rest of the maintenance phase. Tab. 6-mercaptopurine and Tab. methotrexate were given orally throughout the maintenance phase.

The patient who developed testicular relapse during the maintenance phase was diagnosed clinically and confirmed by testicular biopsy. The CNS and bone marrow remission were assessed in every patient. The clinical remission of ITR (return of testicular size to normal with normal hematological profile and no other signs and symptoms of disease) was recorded at the end of induction phase.

Bilateral testicular irradiation was given to testes and inguinal canals by a megavoltage cobalt machine. A total dose of 2400 cGy was given to both testes through a single anterior port encompassing scrotal skin laterally and inferiorly. The required dose was divided into eight fractions and 300 cGy was given to each testis. If still there is testicular enlargement despite receiving 2400 cGy, dose to both testes was increased to 3000 cGy. Event-free survival (EFS) was recorded from date of initiation of treatment to the date of relapse, death, or last follow-up. The analysis of relationship of prognostic features with EFS had confounded by small sample size. Collected data were organized into a statistical format and analyses were done using statistical package for social science (SPSS), a software version 21.0. All continuous data were expressed as mean± SD and categorical data in percentage (%). The p-value of less than 0.05 and confidence interval 95% was taken as the minimum level of significance.

RESULTS

The mean age of ALL children was 4.6±1.2 years. All nine children with ITR were diagnosed clinically, peripheral blood film, bone marrow aspiration (Table1). The distribution of various findings of isolated leukemic child are showed diagrammatically (Figure 1). The histopathological findings showed infiltration of leukemic cell in blood vessels. There was presence of more than 25% leukemic cells in the blood vessels (Figure 2A) and seminiferous tubules (Figure 2B) of the testicular capsule considered as ALL. Initial white blood cell count on average was $33.5\pm3.45x10^9$/L. Immunophenotype showed 77.77% Pre-B and 22.22% T-ALL. All the children had found with blasts cell in peripheral blood film. The bone marrow aspiration findings resemble ALL-L_1 (65%) and ALL-L_2 (35%). During maintenance therapy, 33% of children had relapses before completion of the MRC 841 protocol, and the rest 67% had a relapse within six months of maintenance therapy.

Table 1: Diagnostic criteria of isolated testicular relapse in acute lymphoblastic leukemia (n=9).

Patients	Clinical findings	Hematological findings	Bone marrow	Histopathological findings	Immunophenotype
1	Fever, Hepatomegaly	Hb: 8.75 gm/dl WBC:45.5x10^9/L Platelet:70x10^9/L Blast cell:75%	ALL-L_1	Leukemic infiltrations in blood vessels	T-ALL
2	Fever, bone pain, hepatomegaly	Hb: 9.00 gm/dl WBC:75.5x10^9/L Platelet:40x10^9/L Blast cell:85%	ALL-L_2	Leukemic infiltrations in seminiferous tubules	Pre-B
3	Fever, lymphadenopathy, bone pain, hepatomegaly	Hb: 10.75 gm/dl WBC:30.0x10^9/L Platelet:35x10^9/L Blast cell:35%	ALL-L_2	Leukemic infiltrations in blood vessels	Pre-B
4	Fever, Anemia, bone pain, lymphadenopathy	Hb: 7.75 gm/dl WBC:55.0x10^9/L Platelet:50x10^9/L Blast cell:15%	ALL-L_2	Leukemic infiltrations in seminiferous tubules	T-ALL
5	Testicular swelling, Fever, lymphadenopathy	Hb: 8.25 gm/dl WBC:20.0x10^9/L Blast cell:10%	ALL-L_1	Leukemic infiltrations in seminiferous tubules	Pre-B
6	Fever, Hepatomegaly, bone pain, Testicular swelling	Hb: 9.00 gm/dl WBC:45.5x10^9/L Platelet:55x10^9/L Blast cell:90%	ALL-L_2	Leukemic infiltrations in blood vessels	Pre-B
7	Bone pain, Hepatomegaly, anemia, Testicular enlargement	Hb: 6.50 gm/dl WBC:25x10^9/L Platelet:90x10^9L Blast cell:35%	ALL-L_2	Leukemic infiltrations in seminiferous tubules	Pre-B
8	Anemia, lymphadenopathy, hepatomegaly, bone pain	Hb: 8.75 gm/dl WBC:45.5x10^9/L Platelet:30x10^9/L Blast cell:55%	ALL-L_2	Leukemic infiltrations in seminiferous tubules	Pre-B
9	Anemia, testicular swelling, bone pain, hepatomegaly	Hb: 7.75 gm/dl WBC:45.5x10^9/L Platelet:45x10^9/L Blast cell:15%	ALL-L_1	Leukemic infiltrations in blood vessels	Pre-B

With induction of remission and local field irradiation, all the children underwent complete remission. Initially, the children had received 24 Gy irradiation to both testes. Because of persistence testicular enlargement after the initial dose, 44% of the patients required 30 Gy local field irradiation to both testes. The remaining 56% had received only 24 Gy irradiation having no complications (hematological). During twelve months of maintenance therapy, one child had developed hepatitis and typhlitis which was managed accordingly with antibiotics and supportive care, and later on, succumbed possibly due to infections, diarrhea, and electrolyte imbalance. Three children relapsed in bone marrow during the maintenance period and expired at sixteen months of therapy.

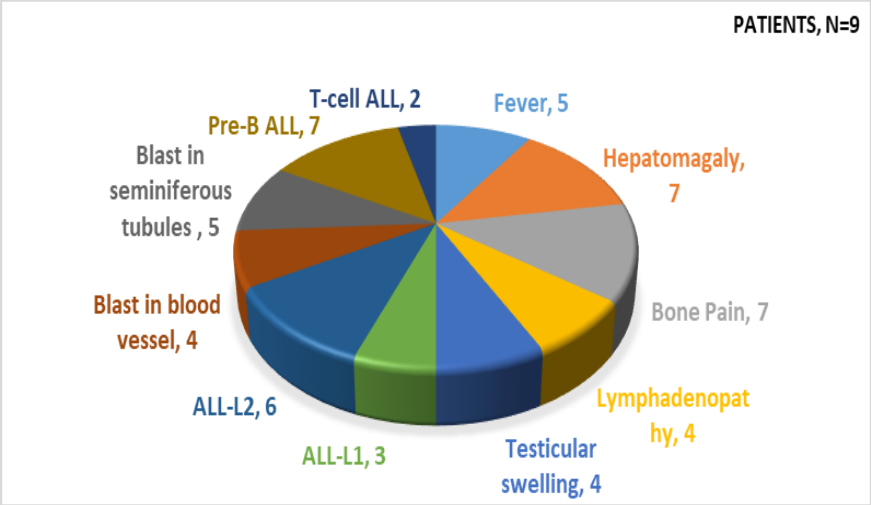
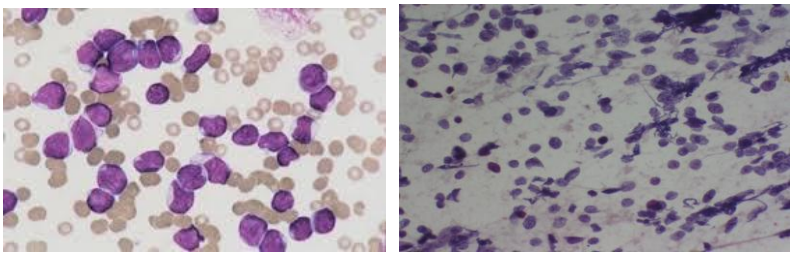


Figure 1: Diagrammatic presentation of isolated leukemic child.

Only five children successfully had completed protocol-based therapy within 24 months. Of these, one child had developed bone marrow relapse following six months after completion of therapy. The other four children were in the second remission after completion of maintenance therapy with disease-free survival (DFS) ranging from 48 to 120 months. Ten years EFS of these children was 43.5% without any significant complications.



(A) **(B)**

Figure 2: Infiltrations of leukemic cells in blood vessels (A) and seminiferous tubules (B) of the testicular capsule (stained with Leishman's and magnified at x 40).

DISCUSSION

Gender remains an important prognostic factor in the treatment of childhood ALL; boys in most studies showed a worse outcome.[23] This may be either due to testes which may be a sanctuary site for the leukemic cells or inadequate systemic treatment. The histopathological examination confirmed five children with infiltrations of leukemic cells in the seminiferous tubules and four with infiltrations in blood vessel. The blood-brain barrier forms an anatomical basis for considering the central nervous system as a sanctuary site. However, there is no clear evidence for such a barrier in tests.

The children are treated with MRC 841 protocol. About 66% of children experienced an ITR before or within six months of completion of chemotherapy. Four of nine children relapsed during the early phase of treatment and eventually developed a second relapse. Three children had a relapse during the maintenance period while one succumbed due to infection and septicemia during the remission phase and the other two were normal up to twelve months and subsequently they relapsed on-off therapy. No significant difference was observed in the outcome between therapy and off therapy of relapses. Our observation differs from Grundy et al., 1997[24] and Wofford et al., 1992[25] where relapse during off therapy had a better outcome than relapses during on therapy. We do agree with the authors.

Fever and bone pain were the common presentation in most of the child followed by organomegaly. Approximately 10% of children had found occult testicular leukemia when bilateral testicular biopsies were performed just before the elective cessation of chemotherapy.[19,26] Initial reports in outcome after secondary treatment were disappointing. Such patients appeared to have a better prognosis when they are given more intensive chemotherapy.[26-27] We do agree with the authors where isolated testicular relapse with aggressive chemotherapy has a better outcome.

We had observed ten years' EFS of these enrolled children of ALL with aggressive chemotherapy is 43.5% (testicular irradiation and CNS chemoprophylaxis). Our observation did not match with findings of Grundy et al., 1997,[24] who reported EFS of 59% at six years in 33 boys with an ITR. However, the findings are consistent with reports of Finklestein et al., 1994,[28] who

documented a DFS of 43% in a different protocol. Furthermore, etoposide is used instead of doxorubicin during the maintenance period which may have a role in the improved outcome.

It was initially believed that testicular relapse results from residual or resistant leukemia at other sites and heralds the onset of disease.[25] However, it seems unlikely as relapses with testicular involvement appear significantly later than other medullary and extra-medullary relapses.[29] Various intratesticular factors like endothelium and interstitium may locally control penetration and it decreases intra-testicular proliferation of leukemic lymphoblasts and cytotoxic drugs which may become ineffective.[29] The leukemic cells resides in the seminiferous tubules. These dormant cells may eventually proliferate subsequently to produce a testicular relapse in ALL.

It has been suggested that physiological puberty in children changes the permeability of vascular endothelium and the immunosuppressive effect of testes may be an important factor for decreased testicular relapse in an older child compared to younger boys during treatment of ALL.[30] The age of the child in our study was four to eleven years, which may be the cause of increased testicular relapse which should be sought out in the subsequent study.

Testicular relapses either isolated or in combination with a medullary relapse are better than isolated medullary or other extra-medullary relapses.[29] This may be due to local intratesticular regulation of leukemic lymphoblasts is still to be unclarified.

It is well known that germ cell dysfunction is common even with scattered doses of irradiation to testes. However, Leydig cell function appears relatively resistant to chemotherapy and doses of irradiation as high as12Gy. It becomes more likely that once the dose of radiation increases beyond 12Gy and is inevitable with doses above 20Gy.[24] So, isolated testicular relapse should be treated with aggressive chemotherapy or radiotherapy.

We have evaluated the endocrine and sexual function of these patients who survived as they received local radiotherapy to testes in a dose of 24-30Gy. All children during follow-up found normally progressed to puberty without any complications. Hormonal profile two of the five children had found gonadal dysfunction with the evidence of elevated luteinizing hormone (LH) and decreased level of testosterone. One of the children is on testosterone replacement therapy and regular follow-up without any evidence of an adverse effect.

The children with newly diagnosed ALL, leukocyte counts greater than 50,000/cmm^3 and age more than 10 years have been associated with a high chance of relapse.[31-32] Boys with ITR who had these features at diagnosis are found to a significantly poorer response with Pediatric Oncology Group (POG) 8304 protocol. These patients have increased survival when treated with more intensive chemotherapy or bone marrow transplant.[33-34] In our observation only one child had initial white blood cell count 75.5x10^9/L and others had about 50.0x10^9/L. The histopathological findings showed blood vessels and seminiferous tubules irrespective of count. These children received intensive chemotherapy only but no bone marrow transplantation was done because of financial problems.

The role of intermediate-dose methotrexate decreases the incidence of testicular relapse in ALL,[35] and is further substantiated by St. Jude and BFM studies.[8,10] Intermediate dose methotrexate needs to be incorporated as the first-line prophylaxis for testicular relapse. Previously testicular biopsy was done to detect isolated testicular relapses in ALL. However, later it was obsolete because it does not make any impact on subsequent EFS.[36] Testicular biopsies in ALL were done in all the children with specific complaints. Instead, a careful clinical examination of testicles including their size and consistency should be assessed at frequent intervals. During regular follow-up at out-patient department, examination of testes and genitourinary system is mandatory.

CONCLUSION

The ALL children with ITR have a good chance of long-term EFS which should be treated with a multi-disciplinary approach team. The children who survive in the second remission needs close supervision and should be followed-up to intensify appropriate intervention to avert pubertal delay. With aggressive chemotherapy or radiotherapy, isolated testicular relapse in ALL patient has good outcome. The event-free survival of ten years is 43.5% having minimum adverse effects. A further multicenter prospective study in ALL with a large sample size is demanded to observe outcome of ITR.

Limitation of the study

This is a small size single center study.

Follow-up

The children with isolated testicular relapse who survived after complication of radiotherapy or chemotherapy was on regular follow-up at out-patient department or sometimes they were contacted over telephone. Routinely patients were observed for anemia or any signs and symptoms of medullary or extramedullary relapse by estimating complete blood count, serum lactate dehydrogenase, chest x-ray, bone marrow aspiration, and ultrasonography of abdomen special attention to genitourinary system. For last ten years the survived children are doing well having no significant complications.

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Ethical Issue
The confidentiality and responsibility of patients have followed the method of the World Medical Association Declaration of Helsinki, 2000.

Conflict of interests
The author declares no conflict of interests.

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