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Late Relapse in a Case of Childhood Acute Lymphoblastic Leukemia

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The development of effective therapy for childhood acute lymphoblastic leukemia (ALL) is one of the undisputed successes in modern oncology. Though it is assumed that children in remission for 6 years after diagnosis are cured(l-3), thereafter relapses do occur, albeit rarely(4-8). We report a case diagnosed to have ALL at the age of 5 years who relapsed 9 years after the initial diagnosis.

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Case Report

A 14-year-old boy presented first at the age of 5 years in May 1985 with complaints of low backache for 3.5 months, fever for 3 weeks and epistaxis for 10 days. The child was found to have marked pallor, sternal tenderness with no significant lymphadenopathy. No hepatosplenomegaly was found. He had a hemoglobin of 95 g/L; total leukocyte count (TLC) 5000/mm^3 and platelets 60,000/mm^3 with a normal peripheral smear. Bone marrow was replaced with 90% lymphoblasts and a diagnosis of ALL (L2 morphology) was made. A cytospin sample of cerebrospinal fluid (CSF) was normal.

The child was induced with vincristine, adriamycin and prednisolone, and later given consolidation therapy with cyclophosphamide and L-asparaginase. Six doses of intrathecal methotrexate and 2000 rads of cranial irradiation were used for CNS prophylaxis. Later, 6-mercaptopurine (75 mg/m^2/day) and methotrexate (15 mg/m^2/week) were given orally for maintenance. Reinforcement was undertaken every 4 months with vincristine, adria-

mycin and prednisolone during maintenance. Strict compliance was ensured and there were no breaks in chemotherapy during the entire period of 3 years. The therapy was stopped in May 1988. The child was followed up regularly till May 1991.

The child presented in May 1994 at the age of 14 years, with history of progressively increasing pallor and body aches for 2 weeks and fever and cough for 2 days; no history of any bleeding episodes or any other localizing symptom for fever was elicited. On examination he had pallor, sternal tenderness; no significant lymphadenopathy, petechiae, ecchymoses or hepatosplenomegaly was seen. Chest examination revealed bilateral crepitations. The left testis was larger than the right, hard in consistency and devoid of testicular sensation. Investigations revealed a hemoglobin of 45 g/L; TLC of 1200/mm^3 and platelets of 40,000/mm^3. Lymphoblasts were seen on the peripheral smear. Bone marrow aspiration showed more than 95% lymphoblasts of L2 morphology. On immunophenotyping, the cells were common ALL antigen (CALLA) positive. Aspiration cytology of left testis showed numerous blasts; cytospin sample of CSF was acellular. A diagnosis of late relapse of ALL with testicular relapse was made. Antibiotics (Vancomycin and Ceftazidime) were given for the chest infection and later he was reinduced with National Cancer Institute, USA multinational protocol MCP 841 for ALL.

Discussion

Various studies have documented that as the length of remission in childhood acute lymphoblastic leukemia increases, the risk of relapse decreases. Investigators at St. Jude Children's Research Hospital demonstrated that after successful completion of 2.5 years of therapy, nearly 80% remained free of the disease. Most of the 20% patients who relapsed did so in the first year off therapy. Recurrence 4 years after cessation of therapy was not encountered(1). Similar results were reported by Chessells(4). In their study, 3 late relapse were encountered. In all these late relapses, there was no evidence of alteration of phenotype.

Analysis of clinical trials undertaken during the last 30 years at St. Jude Children's Research Hospital(2) reveals that intensification of therapy increases the probability of event free survival upto 71%. Most of the treatment failures still occur during the first year off therapy. The risk of recurrence declines to less than 1% three or four years after the cessation of therapy(2). In a large series of patients with first relapse in ALL, the largest period of remission prior to relapse was 7-8 years(7).

In a multi-institutional study on duration of therapy, the Children's Cancer Study Group found that no patients surviving more than 3 years off therapy had relapsed(5). In patients treated according to the BFM protocols, the risk of relapse tapers almost to zero at the end of the fifth year after diagnosis(3). The Indian experience appears to be similar. Advani *et al.* reported a relapse rate of 36% (42/128), of which 80% relapsed while they were on chemotherapy and the rest within a few months after cessation of therapy(9). In the study by Vaidya *et al.* (10), the relapse rate after five years of cessation of therapy was 0.59%. We could not find late relapses occurring 9 years after diagnosis except in a single case report published in 1970 of a child with acute lymphoblastic leukemia who relapsed after 11 years of initial remission(6). One possible reason for the late relapse may be the less aggressive regime for initial therapy used by us in this child.

Various studies suggest that with intensification of therapy, the risk of late relapse decreases(2,3).

Review of literature, therefore, suggests that late relapses do occur but they are rare. These occasional relapses that occur 3-4 year after cessation of therapy suggest that cure may never be certain. In general, it is assumed that most late relapses are recurrences of the disease and not *de novo* events. The biological pattern at recurrence is repeated. At present, the hibernation of individual malignant cells for many years is not readily understood.

With the exception of male sex, older age and possibly bone marrow status on Day 14 of induction therapy, other recognized adverse prognostic factors lose their significance after 2 years from diagnosis and no longer influence the chance of long term survival(4,8). In general, late relapses fare better. Studies suggest that the likelihood of achieving second remission is higher if relapse occurs after successful completion of therapy and if the length of remission is greater(ll,12). The treatment of relapse should include use of various drug combinations preferably those which had not been given earlier.

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