Isolated central nervous system relapse in a child with non-Hodgkin lymphoma during treatment

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Isolated central nervous system (CNS) relapse of non–Hodgkin lymphoma (NHL) is very rare. We report a five-year-old boy with T-cell lymphoblastic lymphoma (T-LBL), who developed CNS relapse under treatment when the primary tumor was in complete remission. The patient presented initially with persistent cough and an anterior mediastinal mass and had no bone marrow or CNS involvement at diagnosis. During re-induction treatment, a routine lumbar puncture revealed blasts in the cerebrospinal fluid (CSF). The patient developed neurological signs and symptoms consequently. Craniospinal radiotherapy followed by BFM (Berlin-Frankfurt-Münster) high-risk chemotherapy protocol was initiated. Despite complete response after three courses, the patient experienced CNS relapse and expired due to disease progression. In the treatment of a NHL patient, routine CSF analysis should be done for tumor cells even when the primary disease is in complete remission.

Key words: non-Hodgkin lymphoma, central nervous system relapse, children, central nervous system prophylaxis.

Lymphoma is one of the most common childhood malignancies, ranking third in the United States and Western Europe and second in Turkey[1,2]. In children, non-Hodgkin lymphoma (NHL) accounts for 45% of all lymphomas, and approximately 15% of them are T-cell lymphoblastic lymphoma (T-LBL)[3]. T-LBL may involve the central nervous system (CNS) (brain, spine and meningeal covering) at presentation or relapse. With current treatment protocols, including CNS prophylaxis, intrathecal chemotherapy and high-dose methotrexate, the CNS relapse rate has decreased dramatically. In the BFM (Berlin-Frankfurt-Münster) series, there was only one isolated CNS relapse in children with T-LBL[4]. In the EORTC (European Organization in Research and Treatment of Cancer) series, only 2 of 119 (1.8%) children with T-LBL had isolated CNS relapse[5]. In this report, we present a child with T-LBL who developed an isolated CNS relapse under treatment despite the early complete response of the primary tumor.

Case Report

A five-year-old boy presented with a 14-day history of persistent cough. His medical and family history was unremarkable otherwise. On the physical examination, pulmonary sounds were diminished on the left lower zone. Laboratory investigation showed a normal blood count, biochemistry and peripheral blood smear. The posteroanterior and lateral chest X-ray and thorax computerized tomography (CT) revealed an anterior mediastinal mass and pleural effusion. Tru-cut biopsy from the mass was consistent with T-LBL. Immunochemistry was positive for CD3, CD34, TdT, and Cd1a. Bone marrow aspiration, bone marrow biopsy and spinal fluid cytology were normal. There were no metastatic lesions in positron emission tomography (PET)-CT. Thus, the patient was classified as stage 3, and treatment with BFM 95-NH protocol was initiated. On the seventh day of treatment, the mediastinal mass had completely disappeared on chest X-ray, and on the 33rd day, thorax CT was consistent with complete response. On the 45th day, the

routine lumbar puncture for intrathecal therapy was performed, and cerebrospinal fluid (CSF) cytology revealed blasts. Immunophenotype of the CSF was consistent with T-LBL. An intrathecal triple treatment (methotrexate, Ara-C, prednisolone) was given, and the use of BFM high-risk regimen was planned. Repeated bone marrow aspiration, craniospinal magnetic resonance imaging (MRI) with contrast, thorax CT, and PET-CT were all normal. In three days, the patient developed signs of CNS involvement like ptosis and somnolence. Due to the neurologic deterioration, craniospinal radiotherapy (RT) with a dose of 18 Gy was initiated immediately. Neurologic signs and symptoms recovered in a week after RT. Consequently, the patient received six courses of high-risk blocks according to the BFM protocol. At the end of the third course, the patient was in full remission; CSF cytology and bone marrow aspiration were normal with no findings of other metastatic lesions. Bone marrow harvesting was done for autologous stem cell transplantation (ASCT). Unfortunately, after the completion of high-risk blocks, the family refused ASCT. Thus, chemotherapy (BFM protocol II phase 1 and 2) was continued. During therapy, CSF cytology was evaluated regularly, and in the fourth week of the treatment, CSF cytology revealed new blasts again. The patient deteriorated neurologically in a few days, developing generalized seizures and loss of consciousness. Chemotherapy consisting of 3 g/m^2 ARA-C, 3 mg/m^2 vinblastine, 20 mg/m^2 dexamethasone, 100 mg/m^2 VP-16, and intrathecal therapy (12 mg methotrexate, 30 mg ARA-C, 10 mg prednisolone) (BFM-CC Block) was initiated. After the first CC block, the patient received two courses of weekly triple intrathecal chemotherapy. Despite the chemotherapy, the patient progressively deteriorated neurologically and expired due to progressive disease.

Discussion

Non-Hodgkin lymphoma (NHL) may involve the CNS, including peripheral nerves, spinal nerve roots, spinal cord, meninges, and brain, at diagnosis or relapse. This may be due to direct invasion or compression of these structures[6]. The prevalence of CNS involvement in children with T-LBL at presentation is 2.5%[5]. Why some lymphomas involve the CNS initially and others do not is not clear. Some adhesion molecules such as CD-56 expression were reported to be associated with CNS disease in lymphomas[3].

Before the 1970s, treatment results of NHL were poor, with five-year survival ranging from 5-33%[3]. However, with the current treatment protocols, reported event-free survival rates are now in the range of 70-90%[7-10]. With CNS prophylaxis including intrathecal and high-dose methotrexate, a high cure and survival rate has been obtained, and CNS relapse rate has decreased dramatically. Thus, cranial prophylactic RT for T-LBL that was used previously has been abandoned over time. With the current treatment protocols, CNS relapse is usually seen concurrently with a bone marrow relapse or other widespread metastasis.

Isolated CNS relapse is rare in patients with NHL. In adults, 1-5% of patients with NHL are reported to develop isolated CNS relapse[11-13]. In the BFM series, there was only one isolated CNS relapse in children with T-LBL[4]. In the EORTC CLG 58881 trial, only 2 (1.9%) of the 119 children with T-LBL had isolated CNS relapse[5]. In our series, consisting of 51 children with T-LBL, this is the first case with isolated CNS relapse.

Response to the pre-phase to chemotherapy is a very important prognostic factor for T-LBL[3,5]. The Children's Leukaemia Group reported a 100% event-free survival at six years for complete responders after seven days in contrast to 14% in non-responders[5]. Our case developed an isolated CNS relapse despite a complete response on the 8th day.

In the literature, most of the CNS metastases in adults (63%) are seen as lymphomatous meningitis. Parenchymal metastases or combined meningeal and parenchymal involvement is rarer[14]. In our case, CNS involvement was consistent with the literature. There was no sign of parenchymal involvement in the cranial MRI.

Previous studies have shown that the majority of relapses occur in the first year after remission[14]. Our case developed CNS relapse after the first month of treatment while still on treatment. This may be due to undetected subclinical disease initially, which is suggested by the high rate of CNS involvement within six months of initial therapy in patients with aggressive NHL. In addition, late CNS

recurrences of NHL may represent second primary tumors in previous years.

In conclusion, although CNS prophylaxis has dramatically decreased the CNS relapse rate in children, every routine CSF taken during intrathecal therapy should be evaluated by cytology, and every neurologic sign or symptom should be evaluated for CNS involvement even in the presence of remission of the primary tumor.

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