The Turkish Journal of Pediatrics 29:171 - 176, 1987

LEUKEMIAS ASSOCIATED WITH NEUROFIBROMATOSIS IN CHILDREN*

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Key words: acute lymphoblastic leukemia, chronic myeloid leukemia, neurofibromatosis

Malignancies such as brain tumor, neuroblastoma, Wilms' tumor, melanoma, hepatoma and leukemia have been reported to be associated with neurofibromatosis[1,2].

Leukemia associated with neurofibromatosis was first reported by Royer et al[3] in 1958. Subsequently, this association has been shown not to be rare[4-14]. Although chronic myeloid leukemia (CML) is rarely seen in the pediatric age-group, when it does occur, it is frequently associated with neurofibromatosis[9-11,14].

In this paper, we present five children with neurofibromatosis in which CML was present in three and acute lymphoblastic leukemia (ALL) in two.

Case Reports

Case 1

A five-year-old boy was admitted to Hacettepe Children's Hospital in 1977 with complaints of pallor and abdominal distenson. He had been in good health 40 days prior to his admittance. Physical examination revealed one café-au-lait spot measuring 5×5 cm and many others 1.5 cm in diameter scattered over his abdomen and extremities. The liver was palpable ten cm below the costal margin and the spleen was felt four cm below the left costal margin. Moderate enlargement of the inguinal axillary and submandibular lymph nodes were noted.

The patient was diagnosed as having CML according to examination of peripheral blood smear, bone marrow and other laboratory findings. Hematological data

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including the leukocyte alkaline phosphatase and hemoglobin F values are shown in Table I. Many café-au-lait spots were also present on the patient's mother.

The child had recurrent attacks of bronchopneumonia during the follow-up period. Although immunosuppressive therapy was started, no response was obtained. Two years later the patient died at home.

Case 2

A two-year-old boy was admitted to Hacettepe Children's Hospital in 1984 with complaints of abdominal distension, irritability and anorexia which had started four months prior to his admission. On physical examination he was irritable and eight café-au-lait spots were present on his body, one of which measured 8×6 cm and the others at least 1.5 cm in diameter. The patient had enlarged cervical, axillary and inquinal lymph nodes and massive hepatosplenomegaly. The patient's mother had multiple café-au-lait spots and fibromas which had been confirmed by biopsy. An intravenous pyelogram of the patient revealed a double collecting system.

The child was diagnosed as having CML according to the data obtained from the peripheral smear, bone marrow and other laboratory findings. This patient had frequent attacks of lower respiratory infections. Chemotherapy was started. A reduction in spleen size was accompanied by a decrease in the WBC count and an elevation in the platelet count.

Case 3

A five-month-old male infant was admitted to Hacettepe Children's Hospital in 1984, who had been febrile over an extended period of time. Physical examination revealed that the infant was not in good health. Megalocornea, blue sclera, low-set malformed ears, right hydrocell and seven cafe-a-lait spots, each measuring at least 1.5 cm in diameter on his abdomen and legs and hepatosplenomegaly (liver six cm and spleen eleven cm) were present. There was also bilateral enlargement of the cervical lymph nodes.

Two café-au-lait spots, one measuring two cm in diameter and the other five cm were seen on the patient's mother. Table I shows some of the patient's laboratory findings.

The infant was diagnosed as having CML and neurofibromatosis. Since the parents refused chemotherapy treatment for their child, he was discharged and died at home one week later.

Case 4

A four-year-old boy was admitted to our hospital in 1985 with complaints of back pain and pallor. He had had pallor for three months and pain in the legs 15 days prior to admission. On physical examination he was irritable and pale. Ten

TABLE I: Hematologic Data of the Patients

Case No.	Age	Sex	Hb (g/dl)	WBC (10^9/L)	Thrombocytes (per mm^3)	Peripheral pro	Peripheral mye	Blood meta	Smear neut	Lymphocytes	Monocytes	Blast cells	Leukocytes alkaline phosphatase (Unit)	HbF (%)	Type of leukemia
1	5	M	8.9	48,000	88,000	1	–	19	45	33		2	36	31	CML
2	2	M	10.5	67,200	60,000	26	9	15	29	9	5	7	24	20	CML
3	5/12	M	6.8	163,000	40,000	12	23	14	5	15	4	27	31	35	CML
4	4	M	6.7	4,000	rare			lymphoblasts					–	1.6	ALL
5	20/12	F	5.3	19,000	rare			lymphoblasts					–	–	ALL

café-au-lait spots measuring at least 1.5 cm in diameter were scattered over his trunk and extremities.

The child had multiple englarged cervical lymph nodes and ecchymoses. The patient's mother also had café-au-lait spots. L_1 type ALL was diagnosed from bone marrow examination. The patient was given chemotherapy treatments and he has been in remission for two years.

Case 5

A 20-month-old female infant was admitted to our hospital with complaints of pallor and ecchymoses in 1986. She had enlarged cervical, axillary and inguinal lymph nodes and massive hepatosplenomegaly. Numerous café-au-lait spots were seen over her trunk, one of them measuring 3×3 cm. The infant was diagnosed as having L_1 type ALL. Although chemotherapy treatments were administered, the patient could not go into remission. Table I shows the patient's hematological data.

Discussion

Chronic myeloid leukemia was diagnosed in three of our patients on the basis of clinical findings and also hematological data in which high HbF and low leukocyte alkaline phosphatase values were observed[15]. More than six lesions of café-au-lait spots, each larger than 1.5 cm in diameter were found in all the patients. The mothers of four patients also had café-au-lait spots. In addition o biopsy taken from the mother of Case 2 revealed a fibroma.

The results of cytogenetic studies carried out were found to be normal in three of our CML patients. As it is known, no remarkable change is observed in juvenile CML. Contrary to this, in adult CML, the Philadelphia chromosome is positive.

Two cases of juvenile CML with a chromosome abnormality have been reported in the literature. In one of these cases, the 46 XY, Y inversion anomaly was detected while in the other, trisomy 8[11,14].

About 40 patients with neurofibromatosis associated with leukemia have been reported in the literature[3,5-9,11-14]. Although CML consititutes from four to five percent of all cases of childhood leukemia, twenty-seven percent of these cases has been associated with neurofibromatosis[11,14]. Approximately 30 CML cases have been diagnosed in our Pediatric Hematology Unit and among these, three were associated with neurofibromatosis. However, leukemia was not observed in 42 patients diagnosed in our hospital as having neurofibromatosis[16].

Although "transient leukemia" with neurofibromatosis is known, it is unlikely that this situation occurred in our three patients with CML, because of their outcome. The follow-up of Case 2 will reveal the prognosis.

Addendum: Just before this article went to print, it was learned that Case 2 had died three years later.

As reported in the literature, we have also seen recurrent pulmonary infections in our CML patients, and at autopsy peribronchial infiltration with immature neutrophils has been observed[11]. In Cases 2 and 3, a double urinary collecting system and multiple malformations such as megalocornea and low-set malformed ears were present. Congenital malformations have been documented with neurofibromatosis, however, megalocornea and congenital glaucoma are extremely rare[17].

In conclusion, we suggest that since there is a frequent possibility that leukemia occurs in association with neurofibromatosis, very close follow-ups with blood counts should be carried out in patients with neurofibromatosis.

Summary

Five patients with leukemia associated with neurofibromatosis are presented. All the patients had café-au-lait spots, a classic feature of neurofibromatosis. Three patients had juvenile-type chronic myelocytic leukemia and two acute lymphoblastic leukemia.

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