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A RARE ENTITY AMONG CHILDHOOD MALIGNANT LYMPHOMAS*

(Large Anaplastic T-cell Ki-1 +)

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SUMMARY: Ulukutlu L, Hitzig W, Maurer R. (Department of Pediatrics, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey). A rare entity among childhood malignant lymphomas (large anaplastic T-cell ki-1 +). Turk J Pediatr 34:37-41, 1992.

A case of peripheral type T-cell lymphoma is presented to underline the difficulty in distinguishing the initial clinical findings of an inflammatory neoplastic disorder since the diagnosis could only be arrived at after several repeated lymph node biopsies.

An 11 10/12-year-old boy admitted to the hospital with inguinal lymph node enlargement was diagnosed as having adenitis and periadenitis. The disease had progressed and the patient had remittent fever rising to 39 °C, and another biopsy was taken. Cervical lymphadenomegaly was present, A diagnosis of chronic lymphadenitis with lymphocyte loss and fibrosis was established.

The diagnosis could only be made from biopsy material taken from the deep cervical (jugularis interna) and axillary lymph nodes one year later, which showed Ki-1 antigen positive large T-cell lymphoma.

The disease showed continuous activity in spite of chemotherapy and the child survived only 17 months. *Key words: lymphoma, large cell KI-1 + lymphoma, peripheral T-cell lymphoma*

The diagnosis of non-Hodgkin's lymphoma, the most frequent malignancy occurring in childhood after leukemia, can be established by the histopathological findings of a lymph node biopsy. However, the differential diagnosis between a malignancy and an infectious process may be difficult during late childhood, as in the case presented. We present this rare entity with the aim of underlining the importance of subtypes in the prognosis and treatment and possible insufficiency of a histopathological diagnosis in addition to emphasizing the cooperation between different centers which has become essential in view of the diagnostic importance of cell markers and monoclonal antibodies[1,2].

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Case Report

An 11 10/12-year-old boy, the elder of two brothers, was referred to the Pediatric Oncology Department of the Cerrahpaşa Faculty of Medicine at the end of January 1988 for evaluation of fever and enlarged cervical and inguinal lymph nodes. Past history of the patient and family history were unremarkable. Immunizations including BCG were given at the appropriate intervals.

Lymph node enlargement in the left inguinal region was first recognized in November 1987, and was biopsied and diagnosed as acute adenitis and periadenitis. A repeat lymph node biopsy of the left cervical and inguinal regions was performed in January 1988, but this time an evaluation of chronic lymphadenitis with lymphocyte loss and fibrosis was made. Ampicillin, gentamicin and penicillin were administered for a pharyngeal infection. The fever dropped in the evenings with daily elevations ranging from 37 °C to 39.2 °C.

Physical examination revealed a boy with normal somatic development. Multiple pigmented nevi of various sizes were present on the back. Biopsy incision sites were visible on the left inguinal and cervical regions, the latter still showing fresh granulation tissue. A 3 × 4 cm, firm, fixed and painless swelling (lymph node packet) was palpable in the left cervical region. The tonsils were hyperemic and hypertrophic. Other systemic findings were normal.

Laboratory findings revealed a hemoglobin of 13 g/dl, hematocrit 40 percent, white blood cells 23 × 10^8/L, a differential count with 5 percent band forms, 58 percent polymorphonuclear leukocytes (with coarse cytoplasmic granulation), 2 percent eosinophils, 3 percent monocytes and 32 percent lymphocytes. Reticulocytes were 2.3 percent and platelet count 270 × 10^8/L. The erythrocyte sedimentation rate was 65 mm/hour.

Serum copper concentration was 210 µg/dl, fibrinogen 592 mg/dl, alkaline phosphatase activity 150 U/L, lactic dehydrogenase activity 300 U/L, IgG 1900 mg/dl, IgA 263 mg/dl, IgM 261 mg/dl with decreased alpha-2 and gamma globulin at protein electrophoresis.

Endotoxin stimulated nitroblue tetrazolium (NBT) was 74 percent and the tuberculin test was negative. The bone marrow examination was consistent with anemia and infection. Few white blood cells were detected in the urine sediment. The chest X-ray was normal. Computerized tomographic examination of the thorax and abdomen showed thymic hyperplasia, hepatomegaly and enlargement of the extrarenal pelvis.

On the seventh day of admission, red, tender masses appeared in front of and behind the cervical swelling and additional bean-sized lymph nodes were palpable bilaterally in the cervical and axillary regions. Cefazolin was administered intravenously. No material could be obtained upon incision of the fluctuant

appearing left cervical biopsy site and no response could be obtained after the administration of various antibiotics.

After contact with Zurich Children's Hospital, it was decided that the patient be reevaluated for chronic granulomatous disease and referred for a repeat biopsy, if necessary. On examination at Zurich Children's Hospital in February 1988, the patient was found to be mildly obese and extremely pale with enlarged right cervical, axillary, occipital and bilateral inguinal lymph nodes and also presented with left supraclavicular and cervical multiple masses. The apple-sized swelling with an incomplete biopsy scar was fixed to the underlying tissue. The liver and spleen were palpable 5 and 2 cm, respectively below the costal margin. The chest X-ray showed a normal mediastinum and ultrasonographic examination of the abdomen indicated splenomegaly and only two lymph nodes at the origin of the arteria mesenterica superior. Deep cervical (jugularis interna) and axillary lymph node biopsy specimens were diagnosed as being large cell mesenchymal, histiocytic, lymphoblastic tumor (T-cell lymphoma).

Immunohistochemical examination of the tumor tissue with antibodies against Ki-1 (activated T and B lymphocytes) showed evident positivity in the tumor tissue and in the intact subcapsular and peritrabecular sinus areas of the lymph node. Due to mild positivity with Uchl (T-cell marker) and the negativity with MB2 (B-cell marker) in the tumor tissue, the tumor was most probably a large cell anaplastic T-cell lymphoma. Leukocyte common antigen was positive in the lymph node tissue and slightly positive in the plasma cells in the tumor tissue. Factor 8 rAg was negative in the tumor.

When the histological diagnosis was almost certain, chemotherapy was initiated and the fever dropped promptly. The induction course was completed with four weeks of a modified ACOP regimen (adriamycin, cyclophosphamide, vincristine and prednisolone). Since leukopenia developed following the initiation of chemotherapy, this treatment had to be interrupted for short periods during which time mild fever, cervical, axillary and inguinal lymphadenomegaly, a maculopapular rash and hepatomegaly 1.5 cm below the right costal margin were observed on physical examination. During maintenance therapy, consisting of three-week-cycles, the patient had a relapse. Bone marrow examination revealed myeloid hyperplasia and erythroid hypoactivity. The hili were prominent and increased left paravertebral density was seen on the chest X-ray. Abdominal ultrasonographic examination revealed multiple small lymph nodes under the liver, at the hili of the liver and spleen and mild splenomegaly. Due to histiocytic predominance, the Pro-MACE scheme including VP-16 (adriamycin, cyclophosphamide and prednisolone) was administered. As a result of this treatment, the fever and the rash disappeared and the lymph node enlargement regressed considerably.

In spite of the chemotherapy, the disease is probably still active. In view of recent reports concerning Ki-1 antigen positive large T-cell lymphoma[3,4], the patient's treatment was reevaluated at relapse when typical, locally recurring manifestations were observed in February 1989. Since the disease has been reported to have responded favorably to the regimens used in treating acute lymphoblastic leukemia (ALL), the ALL protocol of the International Society of Pediatric Oncology (SIOP) 79/84 (cyclophosphamide, vincristine, prednisolone, methotrexate, L-asparaginase, cytosine arabinoside and thioguanine) was administered. Manifestations of the disease disappeared. However, bilateral cervical and right axillary lymphadenomegaly, rash and fever recurred soon after completion of induction. The occurrence of lymphomatous activity following the administration of L-asparaginase suggested a resistance to the drug. Hepatomegaly, initially indirect and later direct hyperbilirubinemia, splenomegaly and ascites appeared. The use of high-dose steriods and later additional cytosine, arabinoside and thioguanine were not able to prevent the patient's death. The duration of survival was 17 months.

Discussion

Large cell T-cell lymphoma of the anaplastic type is a new entity, which is now differentiated from early histiocytic malignant lymphomas. The involvement of peripheral lymph nodes without associated mediastinal involvement is typical. This type of lymphoma might present as either an infectious or a neoplastic process.

Although rare, recent reports point to the existence of peripheral T-cell lymphoma in childhood[3,4]. The monoclonal antibody Ki-1 shows a selective reactivity to the Reed-Sternberg cells seen in Hodgkin's disease. In differentiating the anaplastic type of diffuse large cell lymphoma (peripheral T-cell lymphoma) from other histiocytic lymphomas, the presence of Ki-1 antigen is clearly diagnostic. Large cell anaplastic Ki-1 positive lymphoma in childhood clinically differs from malignant histiocytic lymphoma with initial peripheral lymph node or extra-nodal involvement and no central nervous system or bone marrow invasion. It has been suggested that a translocation at the q35 site of the fifth chromosome could be specifically associated with Ki-1 positive lymphoma and has a causal role aside from these histopathological characteristics[5].

In a study carried out on 15 children (age range 9-15 years) between 1975-1986, Gasparini et al[3] reported that most of these patients, in whom immunohistochemical examination of paraffin sections showed Ki-1 antigen positivity, had been febrile with dermatological manifestations. In 1989 Leake et al[4] also reported large cell anaplastic Ki-1 positive tumors in three of six children (median age 9.5 years) with peripheral T-cell lymphoma. The disease was extranodal in two of

these patients. Our patient showed a similar clinical picture to the patients reported in the literature[3,4]. These patients were initially treated with the CHOP (cyclophosphamide, hydroxylurea, oncovin, prednisolone) regime which was also applied to our patient, and they later used the UKALLx regime (daunorubicin, cytosine arabinoside, thioguanine, VP-16) protocols.

The case presented clearly illustrates that it is at times difficult to differentiate peripheral type T-cell lymphoma from an inflammatory neoplastic disorder. Histopathological examination of lymph nodes coupled with the use of cell markers and monoclonal antibodies are of importance in the establishment of a specific final diagnosis.

REFERENCES

1. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 66:848, 1985.
2. Kadin ME, Sako D, Berliner N, et al. Childhood Ki-1 lymphoma presenting with skin lesions and peripheral lymphadenopathy. *Blood* 68:1042, 1986.
3. Gasparini M, Gianni C, Morandi F, et al. Large cell Ki-1 + lymphoma of children. *Med Pediatr Oncol* (Abstr XXI SIOP meeting) 16:406, 1988.
4. Leake J, Kellie SJ, Pritchard J, et al. Peripheral T-cell lymphoma in childhood. A clinicopathological study of six cases. *Histopathology* 14:255, 1989.
5. Rimokh R, Magaud JP, Berger F, et al. A translocation involving a specific breakpoint (q35) on chromosome 5 is characteristic of anaplastic large cell lymphoma (Ki-1 lymphoma). *Br J Haematol* 71:31, 1989.