SECOND NEOPLASMS are beginning to be recognized as a risk in the treatment of malignant disease. Acute lymphoblastic leukemia of childhood (ALL) in many patients can be treated effectively, and it is not surprising that second neoplasms should occur in some patients.

The present patient is remarkable because of the tumor histology, its clinical presentation, and the extremely long interval between the original disease and the appearance of the second tumor.

CASE REPORT

L.Z. was born on June 24, 1959. At 40 mo of age (October 29, 1962) she was presented to one of us (S.L.L.) with a history of fever, pallor, and anorexia for 10 days. Hepatosplenomegaly and ecchymoses over the upper limbs were found. The hemoglobin was 3.5 g/dl, the white cell count 29 x 10^9/liter with 59% lymphoblasts, and the platelet count was 18 x 10^9/liter. The bone marrow was hypercellular with 99% lymphoblasts (Fig. 1).

She was treated according to ALGB protocol 6205, receiving 6-mercaptopurine (50 mg) and prednisone (25 mg daily by mouth) for 24 days. She responded promptly, achieving complete remission after 2 wk. Maintenance therapy was begun immediately with 6-mercaptopurine, 50 mg/day, and methotrexate, 2.5 mg daily. Two doses of intrathecal methotrexate were also given as part of a randomized study of its value as prophylaxis. Ten days later, an aplastic bone marrow was found, and she was hospitalized with Aerobacter aerogenes sepsis. Following recovery, treatment was resumed at half the dose used in the previous dose until 1967 when the original dosage was reinstituted. In October 1970, all treatment was stopped.

Growth, development, and hematologic follow-up was normal until February 1977, when insomnia and anorexia appeared. She was anemic (Hb, 9g/dl, MCV, 73). As she gave a history of hypermenorrhea, oral ferrous sulfate was prescribed. Seven months later, she returned complaining of productive cough, fever, and malaise. Physical examination was normal, but she had failed to gain weight since her last visit. The hemoglobin was 9 g/dl, the MCV 67, and the white cell count 16.8 x 10^9/liter.

with 85% polymorphonuclear neutrophils. Bone marrow appeared normal with increased iron stores. The chest x-ray showed an infiltrate in the right upper lobe and enlargement of the cardiac silhouette. She was hospitalized. Subsequent chest x-rays exhibited cavitation of the infiltrate. An extensive work-up gave no clues to the probable etiology. The serum gamma globulins were 1.8 g/dl, and the immunoelectrophoresis was normal.

Skin testing was positive for varidase, streptodornase, and negative with PPD, Candida, and mumps.

On the 43rd hospital day, she underwent a right thoracotomy. A large cavitating mass was found involving the right upper lobe and extending into the upper mediastinum and pericardium. It was partially excised. The pathologic diagnosis was anaplastic histiocytic lymphoma (Fig. 2). A suspension of cells made from one of the excised and involved lymph nodes was tested for rosette formation with sheep erythrocytes and for surface immunoglobins. The cells were negative for both markers. She recovered uneventfully.

A lymphangiogram was normal, as were liver and bone scans. A ^6^Ga total-body scan lighted areas of the lung and posterior mediastinum but showed no foci below the diaphragm. The involved areas were radiated, but as spreading of the disease towards the pericardial areas occurred, chemotherapy was started.

The therapy included 6 mo of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP). A complete response was achieved, and clinical restaging showed no evidence of residual disease.

DISCUSSION

Two neoplasms of hematic tissue in the same patient 15 yr apart are probably related—but how? Was the second a direct end-result of the first, or was treatment for the leukemia oncogenic or is the patient inherently more susceptible to lymphoid neoplasms? A search of the literature yields few clues. Localized relapse of acute lymphoblastic leukemia after long survival (over 5 yr) has been described by Burchenal.1 However, the interval between diagnosis and recurrence is much longer in the present subject than in any of Burchenal's patients, and the clinical and histologic presentations are also different.

Hodgkin's disease has been reported to follow ALL after short remissions (10–22 mo) in four patients.2,4 Second neoplasms have been found during autopsy of patients with ALL: carcinoma of the pancreas,5 reticulum cell sarcoma of the brain,6 and a pituitary astrocytoma.7 These findings were incidental on all occasions.

Histiocytic lymphoma has been reported as a complication in patients undergoing renal transplants. The incidence is 350 times more common than in the general population.8 Prolonged immunosuppression is
felt to be the predisposing cause, and the longer the treatment, the higher the incidence of this tumor.

This tumor has also been reported as a complication in patients treated with radiotherapy and chemotherapy for Hodgkin's disease. Although the second tumor occurred 44–124 mo after diagnosis, these patients had been retreated for their Hodgkin's disease during these periods.

No definite conclusion can be drawn about the nature of the relationship between primary illness and second neoplasm in this or other reported patients. Natural history of disease, immunosuppressive effects of drugs, and innate host susceptibility may all play roles.

The patient has been one of the subjects in a previous paper in which a leukemia cluster detected in Brooklyn is reported. The possibility of a genetic or epidemiologic factor is thus enhanced.

Recent reports of long survival of almost 50% of children with ALL have led to the conclusion that these patients are cured. The findings in our patient should caution those espousing cures in these patients until much longer follow-up periods have been achieved.

REFERENCES

Histiocytic lymphoma fifteen years following remission of acute lymphoblastic leukemia

H Dosik, R Anon, SL Lee, AC Allen and M Krishnamurthy