Bull Yamaguchi Med Sch 30 : 47-53, 1983

Prolymphocytic Leukemia: Report of a Case with Autopsy Findings

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(Received January 10, revised February 3, 1983)

Abstract A case of prolymphocytic leukemia, a rare variant of chronic lymphocytic leukemia, was reported with autopsy findings. The patient was a 65-year-old woman who was clinically characterized by huge splenomegaly, mild lymphadenopathy and red skin eruption due to leukemic cell infiltration. The leukemic cells in the peripheral blood and in the bone marrow had pale bluish cytoplasm and one large prominent nucleolus. Transmission electron microscopy also revealed a chromatin structure intermediate between that of a mature lymphocyte and that of a lymphoblast. Surface marker studies suggested T-cell origin. Irradiation to the spleen and chemotherapy with cyclophosphamide, prednisolone and vincristine failed to induce remission.

Key Words: Prolymphocytic Leukemia, T-cell, Combination Chemotherapy

Introduction

Prolymphocytic leukemia, a rare variant of chronic lymphocytic leukemia, was first designated by Galton et al[1]. Prolymphocytic leukemia has characteristic clinical and laboratory findings, such as marked splenomegaly with little or no lymph node enlargement, very high lymphocyte count, and little or no response to treatments which are usually effective in chronic lymphocytic leukemia[1,2]. The leukemic cells in the peripheral blood smears have a characteristic appearance[1-4]. They are relatively large lymphoid cells with a large vesicular nucleolus, relatively well condensed nuclear chromatin and moderate amount of pale-blue cytoplasm.

Human leukemic lymphocytes can be divided into distinct populations based upon the surface markers. prolymphocytic leukemia and classical chronic lymphocytic leukemia are in most instances of B-cell origin[1-3,5-11]. This paper documents a patient with prolymphocytic leukemia of T-cell origin.

Case report

The patient, a 65-year-old woman, was born and had lived in Ube, the western

part of Honshyu island of Japan. She was well until March 1979, when tonsillar enlargement and lymphadenopathy developed and she entered a hospital. Splenomegaly and leukocytosis were found. During the hospital course, red eruption appeared on the face and chest wall. She was referred to us for further examination and treatment.

The mother of the patient had died of a splenic disease.

On admission, her body temperature was 37.6°C, and the pulse 96. The blood pressure was 120/60 mmHg. Physical examination revealed small erythematous macules on the face, chest wall, and lower extremities. The spleen was palpable 3 cm below the level of the umbilicus. The liver edge was palpable 3 cm below the right costal margin. The bilateral cervical lymph nodes were enlarged measuring up to 2 cm in diameter, and most of them were movable and not tender. Marked bilateral tonsillar enlargement was also seen.

The urine was normal. The hematocrit was 21.5%, and the hemoglobin 7.5 g/dl. The leukocyte count was 100,700/mm^3, of which almost all were abnormal lymphoid cells. The platelet count was 89,000/mm^3. The erythrocyte sedimentation rate was 7 mm per hour. The urea nitrogen was 8 mg/dl, the glucose 79 mg/dl, the uric acid 6.1 mg/dl, and the protein 6.4 g/dl (the albumin 2.6 g, and the globulin 3.8 g). SGOT was 23 U, SGPT 7 U, LDH 1,550 U (increased bands 1, 2, 3), and alkaline phosphatase 53 U. X-ray films of the chest revealed calcification of the bilateral hilar lymph nodes. Microscopical examination of the aspirated specimen of the bone marrow showed a hypercellular marrow with a marked increase in abnormal lymphoid elements.

The abnormal lymphoid cells seen in Wright stained films of the peripheral blood are shown in Fig. 1. They have a moderately amount of pale cytoplasm with prominent vesicular nuclei and relatively well-condensed nuclear chromatin. The chromatin pattern was coarser than that of lymphoblast, but not so densely packed as seen in the lymphocyte of classical chronic lymphocytic leukemia. Under electron microscope, the nuclei showed the coarse chromatin pattern and

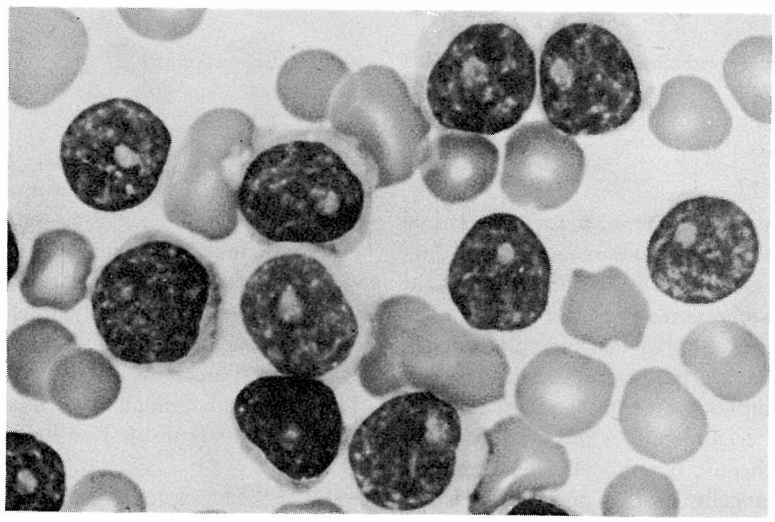

Fig. 1 Most of the leukemic cells in the peripheral blood have a prominent nucleolus and moderate amount of pale cytoplasm. Wright stain.

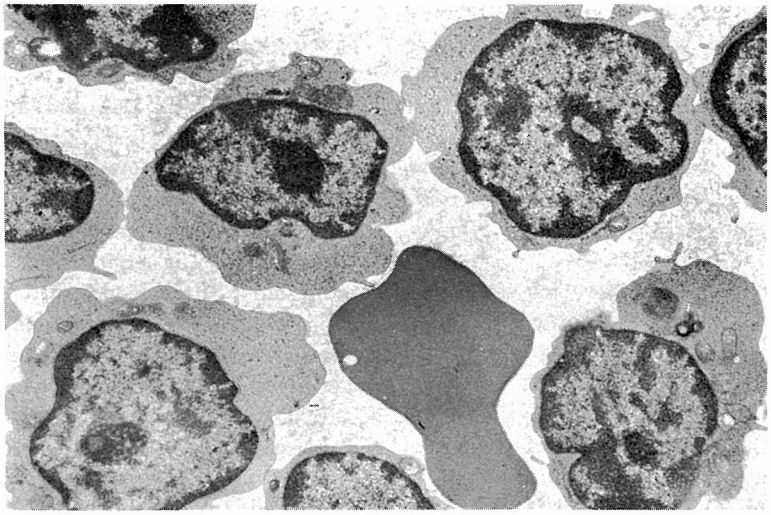

Fig. 2 Transmission electron micrograph of leukemic cells reveals a prominent nucleolus and irregularities of the nuclear contour. ×7700

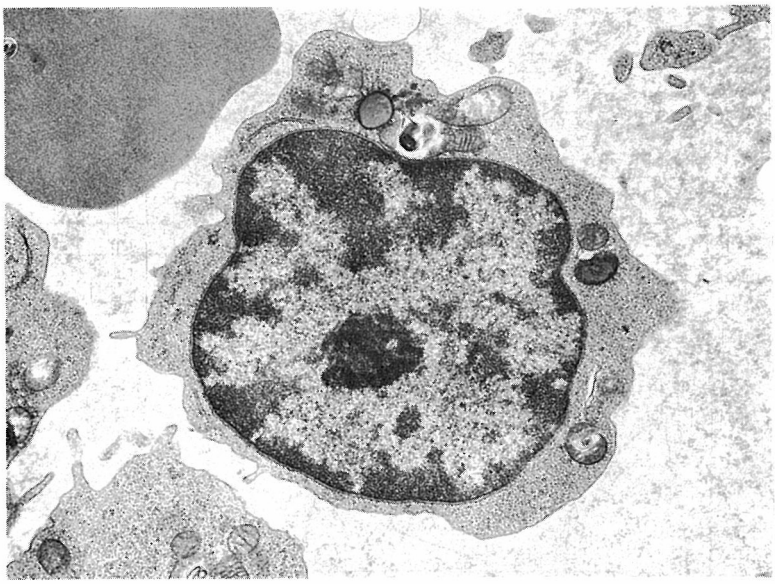

Fig. 3 A prolymphocyte has several cytoplasmic projections, abundant single ribosomes and a nucleus with peripheral condensation of heterochromatin and a prominent nucleolus. ×17000

the nucleoli were large and conspicuous (Fig. 2). The cytoplasm contained a few mitochondria and large number of free ribosomes. The rough endoplasmic reticulums were generally dispersed (Fig. 3). From these findings, the leukemic cells seen in this case were regarded to be prolymphocytes, that had an intermediate characteristic between a mature lymphocyte and a lymphoblast.

These prolymphocytes were not stained by peroxidase nor by PAS staining. Although they were positive for acid phosphatase, they had no resistance to tartaric acid.

Surface marker studies showed that more than ninety per cent of prolymphocytes in the peripheral blood formed both E-rosettes and EAC-rosettes. The cytotoxicity test with anti-T-cell serum was positive. Surface immunoglobulins were not examined.

Skin biopsy disclosed marked infiltration of leukemic lymphocytes in the dermis.

Serum immunoglobulin showed that IgG was 1,000 mg/dl, IgA 190 mg/dl, IgM 80 mg/dl, and IgD 3.0 mg/dl. The complement C_3 was 21.2 mg/dl and C_4 22.5 mg/dl.

From the above findings, a diagnosis of prolymphocytic leukemia was made. The clinical course is summarized in Fig. 4. Irradiation to the spleen and tonsil was started. Prednisolone, 50 mg daily, and cyclophosphamide, 100 mg daily, were prescribed. The white cell count remained more than 100,000/mm^3 except for a transient decrease. The extent of skin involvement was proportional to the white cell count in the peripheral blood. In May, 1980, ascites developed and cytological examination revealed leuke-

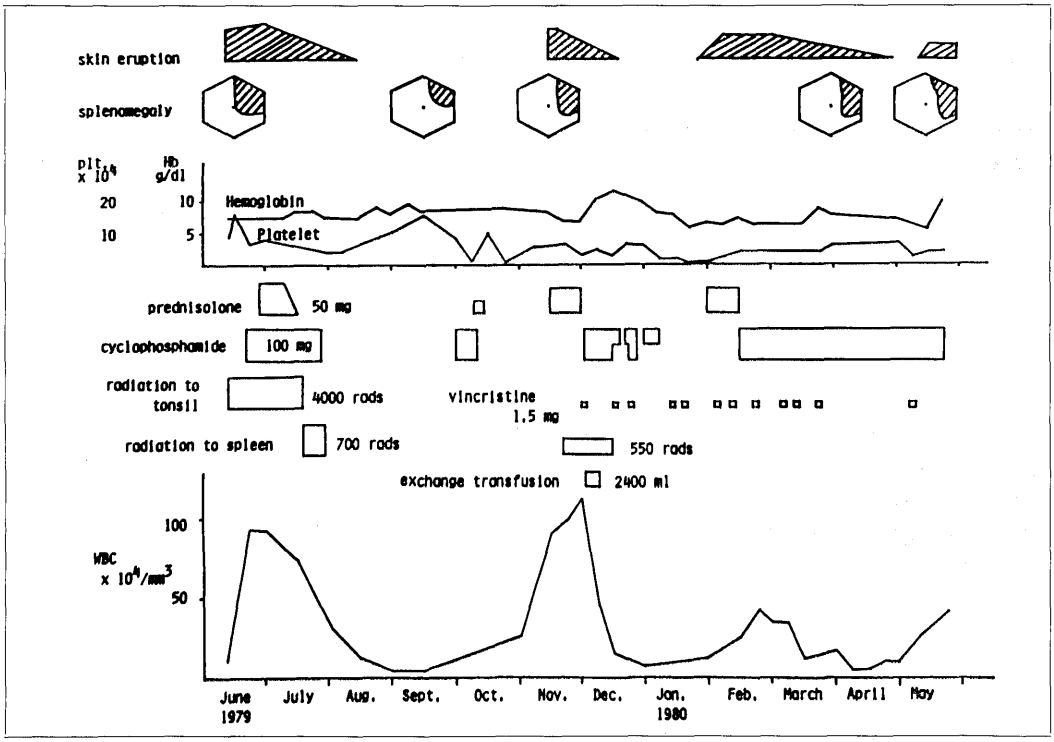

Fig. 4 Clinical course including characteristic clinical symptoms, hematological findings and anti-leukemic treatments.

mic cell infiltration in the abdominal cavity. The patient died of intraperitoneal bleeding on the thirteenth month from the establishment of the diagnosis.

The post-mortem examination showed the followings:

1. Leukemic cell infiltration to the spleen, liver, lung, kidney, esophagus, stomach, intestine, gall bladder, pleura, peritoneum, skin and peritoneal lymph nodes.
2. Splenomegaly (916 g) with anemic infarction.
3. Hepatomegaly (1,710 g) and hemosiderosis.
4. Bleeding foci of the abdominal wall, stomach, intestine, kidney, and left adrenal gland.
5. Bloody pleural effusion on the left side (600 ml).
6. Bloody ascites (1800 ml).

Discussion

Prolymphocytic leukemia, a rare variant of chronic lymphocytic leukemia, is distinguished from classical chronic lymphocytic leukemia and other lymphoproliferative disorders by the characteristic morphology of the lymphoid cells, massivespl enomegaly, inconspicuous lymphadenopathy, and other clinical signs[1,2]. The patient described here had huge splenomegaly and mild lymphadenopathy varing from 1 to 2 cm in diameter. There were moderate anemia, thrombocytopenia, markedly elevated leukocyte count with a large number of lymphoid cells. In common with the morphological features of prolymphocytes originally described by Galton et al[1]., the lymphoid cells seen in this case had moderate amount of cytoplasm with a large vesicular nucleolus and relatively well-condensed nuclear chromatin. There was neither notching nor lobulation in the nucleus. Thus, this case was typical prolymphocytic leukemia on the basis of cell morphology and clinical features.

Surface marker studies in this case showed that a high proportion of the lymphoid cells formed both EAC-rosettes and E-rosettes. As in chronic lymphocytic leukemia, the great majority of neoplastic cells in prolymphocytic leukemia are reported to be B-cell type[1,2,5,6,8,9,12-14,23,24]. Catovsky and his associates[10] reported the first well-documented case of T prolymphocytic leukemia. Recently, populations of lymphocytes having either multiple markers or no detectable markers (null cells) have been observed[7,8,15-17]. Singh et al[7]. reported the prolymphocytic leukemia with both T-cell and B-cell surface markers. It is suggested that lymphocyte maturation involves alloantigenic changes in a circulating stem cell-derived null cell, leading to a cell bearing markers for both T- and B-cells. It is from this latter cell that the classic T- and B-cells ultimately arise[9]. However, even in normal individuals, a small number of lymphocytes (about 2%) forming both EAC- and E-rosettes have been described[15]. Some investigators showed that active T lymphocytes may have C_3 receptors and form EAC-rosettes[18-20]. Although prolymphocytes in our patient formed both EAC- and E-rosettes, strong tendency of skin infiltration and positive cytotoxic test using antithymocyte antibody suggested the possible origin from T lymphocytes. As was pointed out by Singh et al[7]., prolymphocytic leukemia is an identifiable variant of chronic lymphocytic leukemia, but may have heterogeneity that is susceptible to subclassification in the future.

Takatsuki and his coworkers reported a new variant of lymphocytic leukemia, that is, adult T-cell leukemia[21]. This type of leukemia is more common in Japan than in the western countries, and characterized by 1) predominance among natives of Kyushyu and Shikoku, 2) onset in adulthood, 3) subacute or chronic course, 4) lymphadenopathy and hepatomegaly, 5) frequent skin infiltration, and 6) leukemic cells with T-

cell properties characterized by nuclear lobulation or notching. Although the case reported herein clinically resembled adult T-cell leukemia, leukemic cells had neither notching nor lobulation of the nucleus and the morphological features of leukemic cells were not consistent with it.

As for the treatment of prolymphocytic leukemia, various treatment modalities that are usually effective for classical chronic lymphocytic leukemia (splenectomy, irradiation, alkylating agents, and prednisolone) have had little effect in controlling the patient's symptoms or in reducing leukemic cells. In this case, radiotherapy to the spleen and chemotherapy with prednisolone, cyclophosphamide and vincristine were not effective and hematological remission was not obtained. Recently, Reddy et al[22]. reported a case of prolymphocytic leukemia in which asparaginase showed favorable effect in controlling the patient's symptoms. According to Taylor et al[25]., combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) produced an impressive clinical response with rapid reduction of leukemic cells, normalization of the liver size and disappearance of peripheral adenopathy. Early treatment with combination chemotherapy including asparaginase or anthracycline may be worthwhile to try for patients with prolymphocytic leukemia.

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