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We report three patients with chronic lymphocytic leukemia (CLL) who developed malignant lymphomas of unusual character and modes of presentation. Two of the patients had received low doses of chlorambucil for several years before they developed malignant lymphoma, diffuse, large cell type (LCL). In one of these patients LCL manifested as a grossly evident osteolytic lesion. In the second patient LCL developed initially as a localized lesion in the iliac bone. Both patients died within a few weeks after LCL was diagnosed. The third patient, who was found to have CLL during a routine examination, did not receive any therapy for the leukemia. Within six months the patient developed diffuse malignant lymphoma, mixed small and large cell type, with total extinction of the leukemic component. The disease responded favorably to chemotherapy for lymphoma, and the patient is alive with minimal residual disease at this time. Immunohistochemical studies in all three patients suggested transformation or dedifferentiation of the original neoplastic lymphoid clone rather than de novo appearance of another neoplasm. (Henry Ford Hosp Med J 1987;35:251-5)

Chronic lymphocytic leukemia (CLL) in the late stages may cause lymphoreticular and soft tissue tumefaction. The indolent, slowly progressive course of CLL is adversely affected if a "blast" crisis or Richter's syndrome develops.

The three cases reported here represent other unusual examples of dedifferentiation or transformation occurring during the course of CLL.

Case Reports

Case 1

A 74-year-old white male with chronic lymphocytic leukemia had been treated with 2 mg of chlorambucil twice daily for seven years. The initial WBC count at diagnosis was 51,600/μL with 81% small, well-differentiated lymphocytes and 19% polymorphonuclear leukocytes. Hemoglobin was 15.3 g/dL, and platelet count was normal. The patient had no symptoms. Slight splenomegaly was noted, but no hepatomegaly or lymphadenopathy was evident. The physical examination was otherwise normal.

Sternal bone marrow examination at initial diagnosis disclosed 58% small lymphocytes admixed with other normal marrow elements (Fig 1). The lymphocyte count and total peripheral white count dropped significantly with chemotherapy, and physical examination continued to be unremarkable.

Seven years after the initial diagnosis, the patient rolled over in bed and felt sharp pain in his right chest. Physical examination disclosed tenderness in the region of the right seventh and eighth ribs. Radiographs revealed pathological fractures of the posterior parts of the seventh and eighth ribs with destruction of a portion of the eighth rib, suggestive of metastatic disease.

Laboratory studies included hemoglobin of 14.7 g/dL; WBC of 12,300/μL with a differential count of 40% polymorphonuclear cells, 1% eosinophils, 4% monocytes, and 55% well-differentiated lymphocytes; and platelet count of 256,000/μL. Gamma globulin was slightly decreased at 0.42 g/dL (normal 0.6 to 1.4 g/dL). Serum immunoelectrophoresis indicated reduced IgM 22 mg/dL (normal 50 to 250 mg/dL), IgG 412 mg/dL (normal 700 to 1,600 mg/dL), and IgA 58 mg/dL (normal 60 to 300 mg/dL). Other tests, including alkaline phosphatase and coagulation studies, were normal. A radionuclide bone scan demonstrated increased activity in the skull (Fig 2), lower thoracic spine, right distal femur, and left shoulder. Very little bone reaction occurred at these sites, suggesting an aggressive metastatic neoplasm.

Right posterior iliac marrow biopsy showed diffuse infiltration of the marrow by predominantly well-differentiated lymphocytes admixed with other normal marrow elements. Small lymphocytes alone represented 52% of the marrow elements. On the other hand, biopsy from the osteolytic lesion in the right eighth rib showed total obliteration of marrow by a diffuse, noncohesive infiltrate of large neoplastic cells. The cells contained abundant eosinophilic cytoplasm with large round or convoluted vesicular nuclei with several prominent irregular nucleoli (Fig 3). In the touch imprints of the tumor, the nuclear chromatin was fine and reticular. The lesion was interpreted as malignant lymphoma, diffuse, large cell type (LCL). Sections of both CLL marrow and LCL lesion were stained for intracellular Ig heavy and light chains and muramidase by the peroxidase-antiperoxidase (PAP) method of Sternberg (antisera obtained from DAKO). In both lesions the neoplastic cells stained only for IgG heavy chains and Kappa light chains.

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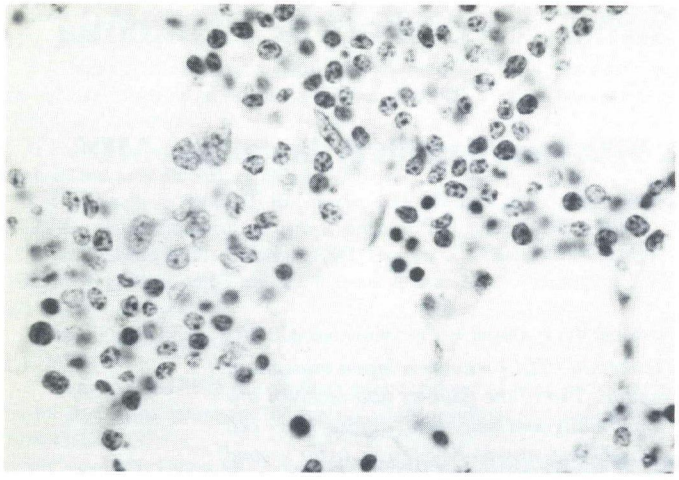

Fig 1 (case 1)—Bone marrow clot section at initial presentation. Note diffuse infiltration of the marrow by small lymphocytes (hematoxylin-eosin stain, X630).

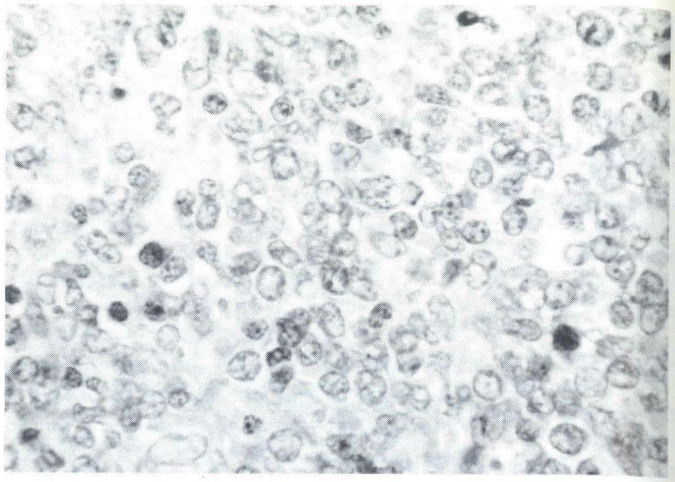

Fig 3 (case 1)—Biopsy of the osteolytic rib lesion. At this magnification, sheets of reticular tumor cells are seen (hematoxylin-eosin stain, X630).

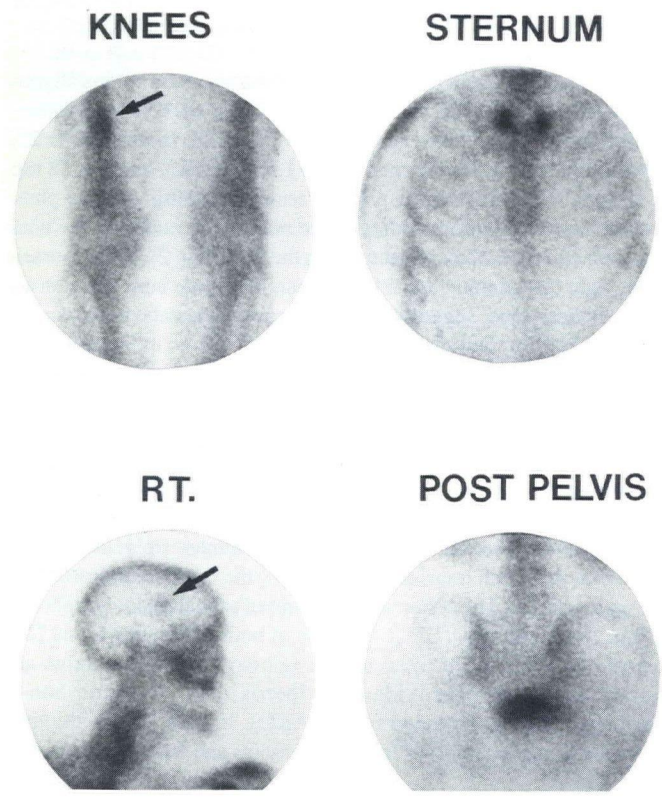

Fig 2 (case 1)—Bone scan showing foci of increased uptake in skull and lower femur (arrows). These were interpreted as metastatic disease.

The cytoplasm of these positively staining cells was filled with coarse granules as well as with clumps of brown material (Fig 4).

Local irradiation therapy to the chest lesion relieved the patient's pain. During the next few months he progressively deteriorated with marked weight loss and anemia. During his last admission he was found to have extensive *Hemophilus* pneumonitis. Hematology profile at this time showed: hemoglobin 10.9 g/dL; WBC 30,700/μL with a differential count of 63% well-differentiated lymphocytes, 22% polymorphonuclear cells, 4% bands, 2% myelocytes, 2% promyelocytes, and 7% monocytes; and platelet count 110,000/μL. Despite vigorous management, the patient succumbed to infection only five months after the diagnosis of LCL was made. Permission for an autopsy was refused.

Comment

The patient had received six years of chlorambucil therapy for CLL before he developed multiple osteolytic lesions due to LCL. At the time of the lymphomatous transformation, a significant number of immature cells were not demonstrated in the peripheral blood. Iliac marrow biopsy and aspirate smears were still characteristic of CLL. These features are akin to a local blast crisis which occurs on occasion in chronic granulocytic leukemia. Based on the nature of presentation, we feel that the term LCL is more appropriate than the terms "blast crisis in CLL" or Richter's syndrome.

Reviews of the reports of LCL or Richter's syndrome associated with CLL indicate that central lymph nodes and liver are most commonly involved (1,2). The bone marrow when involved by LCL shows very small microscopic foci of tumor. Grossly recognizable lesions are rare, while destructive osteolytic lesions due to LCL have not been reported (1). Since immunohistochemical studies on the CLL cells as well as LCL cells of this case showed similar immunologic markers, we presume there was a dedifferentiation/transformation of the same B-lymphoid clone rather than a second de novo lymphoid malignancy.

Case 2

A 63-year-old white female was diagnosed as having CLL from a routine blood smear and which was confirmed by a marrow aspirate ex-

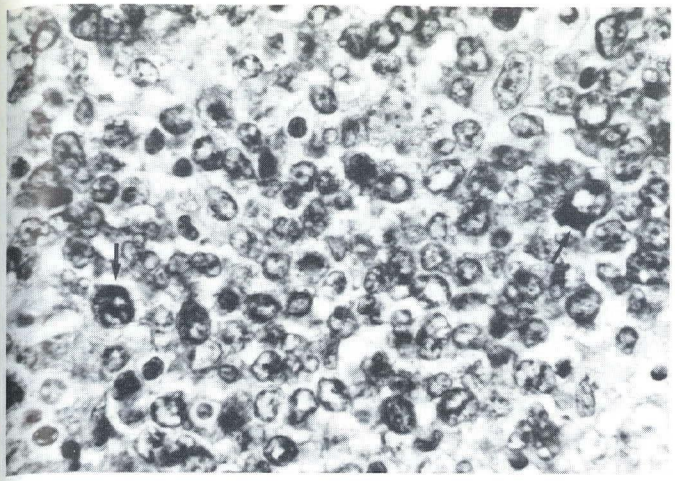

Fig 4 (case 1)—Rib biopsy section. Dark cytoplasmic material (arrows) unmasking IgG in the cytoplasm of LCL cells are frequent (PAP stain, X630). Kappa light chains were also demonstrated in both CLL and LCL cells.

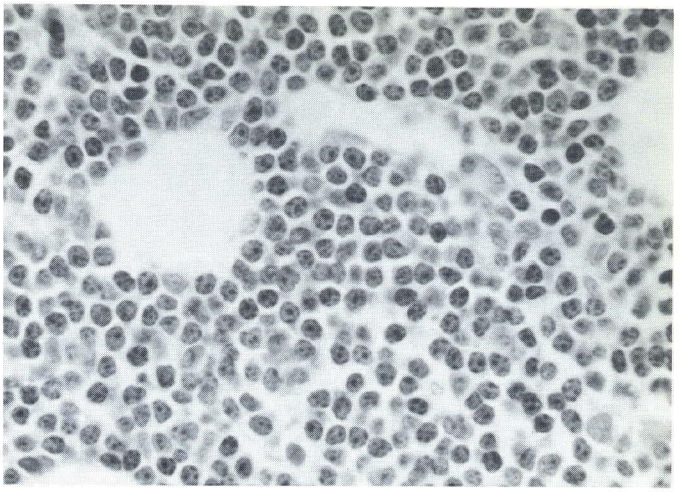

Fig 5 (case 2)—Marrow clot section at initial presentation showing diffuse infiltration of marrow by small lymphocytes (hematoxylin-eosin stain, X630).

amination (Fig 5). Her total leukocyte count was 32,000/μL with 71% well-differentiated lymphocytes. She was asymptomatic with no significant organomegaly or lymphadenopathy. She was treated initially with 2 mg of chlorambucil twice daily, and received this drug for the next four years. On this regimen, her WBC count was maintained between 4,500 and 5,300/μL with normal differential counts. Her only admission to the hospital during these four years was for a transient pleural effusion. Pleural biopsy at that time showed lymphocytic infiltrate consistent with CLL. Hilar adenopathy was also noted then, and the patient received localized irradiation with good response.

Seven years after the initial diagnosis of CLL, the patient was admitted with complaints of fatigue, weakness, and cough. Physical examination was essentially negative. No lymphadenopathy or organomegaly was found. Chest x-ray was unremarkable. Computed tomography showed slight splenomegaly, but no other abdominal masses were seen. Hemoglobin was 8.8 g/dL. WBC count was 3,000/μL with a differential count showing 64% polymorphonuclear cells, 10% bands, 2% metamyelocytes, 1% myelocytes, 1% promyelocytes, 2% eosinophils, 5% monocytes, and 15% lymphocytes. Several nucleated red cells were seen in the smear. An additional finding was the presence of teardrop poikilocytosis. Platelet count was 96,000/μL. These findings were interpreted as consistent with myelophthisic anemia. Marrow aspirate from the sternum showed persistence of many well-differentiated lymphocytes (50%), but a small number of prolymphocytes (9%) and blasts (6%) were also encountered. Granulocytic and erythroid precursors and the megakaryocytes were decreased in the marrow. A repeat marrow aspirate from the left posterior iliac crest showed massive infiltration of the marrow by a monotonous population of large lymphoid cells and a marked decrease in normal hemopoietic elements. The large lymphoid cells contained abundant blue cytoplasm with large reticular nuclei containing several irregular nucleoli (Fig 6). The majority of the nuclei were round and a few were moderately cleaved. In the clot and biopsy sections these lymphoid cells formed distinct noncohesive sheets with large vesicular nuclei and prominent nucleoli (Fig 7); the nucleoli were frequently in

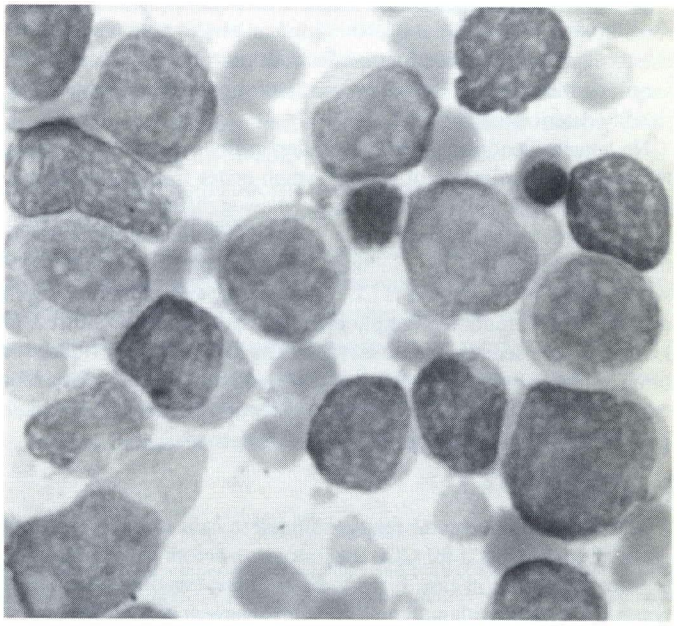

Fig 6 (case 2)—Aspirate smear from iliac marrow showing clusters of large immature lymphoid cells. The cells have adequate cytoplasm, and nuclei show fine reticular chromatin as well as several prominent nucleoli. Nuclear convolutions are seen in a few cells (Leishman's stain, X1000).

apposition to the nuclear membrane. A diagnosis of LCL was made from these findings. Clot sections of the CLL marrow as well as LCL marrow were stained for the presence of surface immunoglobulins, light chains, and muramidase by PAP method. The cytoplasm of both CLL and LCL cells showed positive staining for IgG heavy chains and lambda light chains.

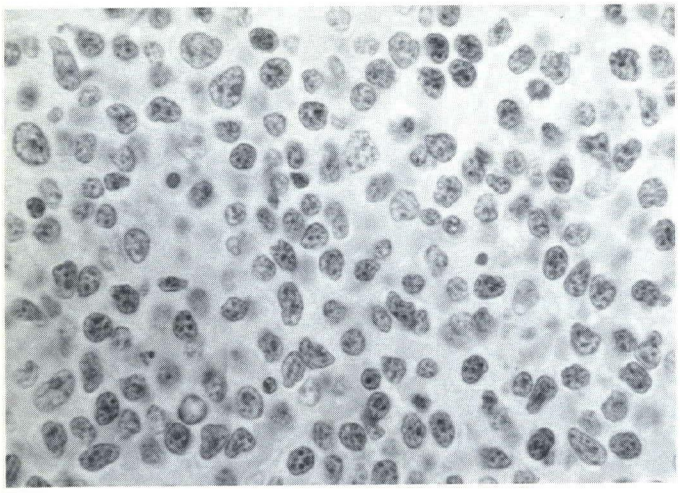

Fig 7 (case 2)—Biopsy of iliac bone marrow showing involvement of LCL. At this magnification, sheets of reticular tumor cells diffusely displacing the bone are seen (hematoxylin-eosin stain, X630).

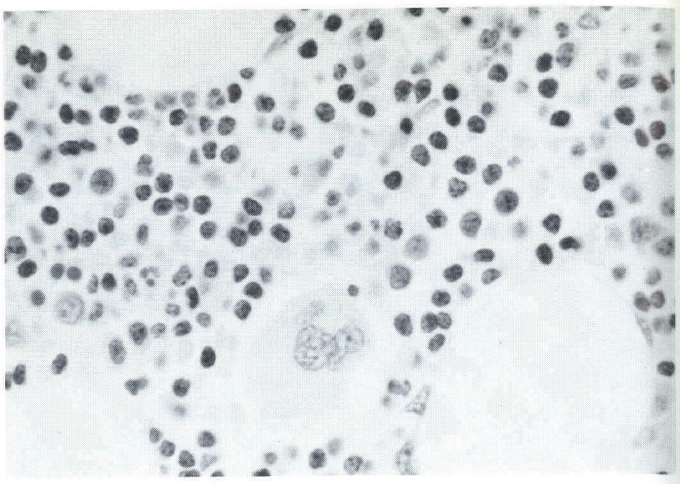

Fig 8 (case 3)—Bone biopsy at initial presentation showing diffuse infiltration of the marrow by small lymphocytes (hematoxylin-eosin stain, X630).

The patient was given a course of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy and then discharged. She returned in two weeks with pancytopenia, fever, and sores in her mouth. Initial blood cultures, sputum cultures, and the chest x-rays were negative for an infectious process. Despite vigorous antibiotic therapy, blood transfusions, and supportive treatment, she steadily deteriorated and died.

No hepatosplenomegaly or lymphadenopathy was seen at autopsy. Histological examination of several lymph nodes from paravertebral, mediastinal iliac, and axillary regions showed diffuse well-differentiated lymphocytic infiltrate with a few pseudofollicular proliferative foci, consistent with CLL. Sections from vertebral and iliac marrow still revealed involvement by LCL. The liver showed a mixture of well and poorly differentiated lymphoid cells in portal triads. Clusters of LCL cells were seen in splenic sections. The lungs showed evidence of bronchopneumonia and focal well-differentiated lymphocytic infiltrates. The rest of the organs were essentially unremarkable. Immediate postmortem blood culture grew *Klebsiella* oxytocoe.

Comment

The patient showed some features similar to case 1. She was on low doses of chlorambucil for CLL for four years before developing LCL transformation. As in case 1, the localized blast transformation in the bones and spleen, without lymph node involvement or acute leukemia, are important differential features from cases of CLL in blast crisis or Richter's syndrome. Immunohistochemical studies suggested a transformation from CLL.

Case 3

A 72-year-old white female, who had a history of villous adenocarcinoma of the rectum, was found to have lymphocytosis on a routine blood examination. The patient was asymptomatic, and the physical examination was essentially unremarkable. Her hemoglobin and red cell indices were normal. Total leukocyte count was 24,000/μL with 75% small, well-differentiated lymphocytes. No further studies or treatment were initiated at this time.

The patient returned to the clinic five years later, and was still asymptomatic. Physical examination revealed mild splenic enlargement. Lymph nodes were not palpable. The remainder of the examination was unremarkable. Blood examination showed hemoglobin 11.4 g/dL with normochromic, normocytic red cells; leukocyte count was 51,000/μL with 91% well-differentiated, small lymphocytes, and 9% polymorphonuclear cells. Other hematologic and chemical parameters were normal. Bone marrow examination showed diffuse infiltration of the marrow with well-differentiated, small lymphocytes (72%) (Fig 8). Maturation of other hemopoietic elements was orderly. No treatment for CLL was given at that time.

During the next few months the patient began to lose weight and suffered episodes of fever and chills. Approximately six months after her previous hospitalization, she was readmitted for evaluation of weakness, weight loss, fever, and swelling in the neck.

Physical examination revealed generalized massive lymphadenopathy and significant hepatosplenomegaly. Cardiovascular and respiratory systems were unremarkable. Laboratory studies showed hemoglobin 9.6 g/dL; slightly microcytic hypochromic red cells; leukocyte count 4,600/μL with a differential of 48% polymorphonuclear cells, 13% bands, 29% small lymphocytes, 6% monocytes, 2% eosinophils, and 2% basophils; platelet count 166,000/μL; and reticulocyte count 2.6%. Prothrombin time and activated partial thromboplastin time were normal. Direct and indirect Coombs' tests were negative. Serum protein electrophoresis was normal. Immunoelectrophoresis showed normal IgG and IgA, but slightly decreased IgM at 40 mg% (normal 50 to 250 mg%). Chest x-ray was negative for an active disease process. Liver and spleen scans confirmed marked splenomegaly. Computed tomography of the abdomen showed massive para-aortic and mesenteric lymphadenopathy. A needle biopsy of the liver showed minimal increase of small lymphocytes in the portal triads which was not diagnostic for leukemia or lymphoma. The cervical lymph node biopsy showed total effacement of the nodal architecture by a diffuse infiltrate of large immature and small cleaved lymphocytes (Fig 9). A diagnosis of malignant lymphoma, diffuse mixed small and large cell type, was made. Studies to demonstrate the presence of immunoglobulin were performed on the clot sections of CLL marrow as well as the lymph node section by PAP method. Material from both specimens showed strong staining for IgG heavy chains and Kappa light chains in the cytoplasm of CLL cells and lymphoma cells.

Iliac marrow aspirate showed only about 14% lymphocytes of which 13% were well differentiated and 1% represented prolymphocytes. Granulocytic, erythroid, and megakaryocytic cell maturation appeared orderly. Clot section did not show any significant abnormality. Bone marrow biopsies from both right and left iliac crests showed large paratrabecular as well as central aggregates of prolymphocytes, lymphoblasts, and large immunoblasts admixed with minor population of small lymphocytes. The cytology was similar to that described in the aforementioned lymph node.

The patient was treated with vincristine, prednisone, and cytoxan. On this treatment, her general condition improved significantly, and lymph nodes as well as spleen showed marked regression. At the time of this report, three and one-half years after the diagnosis of lymphoma, the patient is still being followed in the clinic. No palpable enlargement of nodes, spleen, or liver is now present. A recent repeat bone marrow biopsy still showed persistent lymphocytic infiltrates. The peripheral blood is nonleukemic with a normal total and differential white cell count.

Comment

In this patient, the clinical behavior and morphological features were notably different from the usual encountered cases of CLL. At the time of development of lymphoma the peripheral blood showed normal leukocyte count and differential count. The iliac bone marrow biopsies from both sides showed nodules of poorly differentiated lymphoid cells with normal bone marrow between the nodules. This contrasted with the previous marrow examinations where well-differentiated lymphocytes were diffusely admixed with other marrow elements. A liver biopsy at this time showed no residual CLL. Unlike the classic Richter's syndrome, this patient did not have composite features of CLL and poorly differentiated lymphoma when she developed the transformation. The favorable response to treatment exhibited by this patient is also in sharp contrast to the response of patients with Richter's syndrome, where a majority usually die within a few months.

Thus case 3 is felt to represent a total transformation of an untreated CLL into malignant lymphoma, diffuse, mixed, small and large cell type with extinction of a leukemic component. The favorable clinical response to chemotherapy for lymphoma is interesting. If this patient did not have documented CLL on the previous blood and bone marrow examinations, she would just have been diagnosed and treated as another case of lymphoma.

Discussion

Nonhemopoietic second neoplasms in treated CLL patients are not uncommon (3). In addition, a small number of patients with CLL have shown progression toward acute lymphoblastic leukemia (4,5). In these cases the average interval between the diagnosis of CLL and the occurrence of acute leukemia was about six years. Many of the patients were on various chemotherapeutic regimens including chlorambucil and melphalan. Whenever acute leukemia developed during the course of CLL, it was easily recognized by the presence of a number of blasts in the peripheral blood and by a bone marrow examination.

The cases reported as Richter's syndrome (1,6-8) characteristically develop localized or generalized LCL (reticulum cell sarcoma) during the course of CLL. These patients usually present with massive localized or generalized organomegaly and lymphadenopathy, fever, anemia, lymphopenia, and hypogammaglobulinemia. The prognosis has invariably been poor.

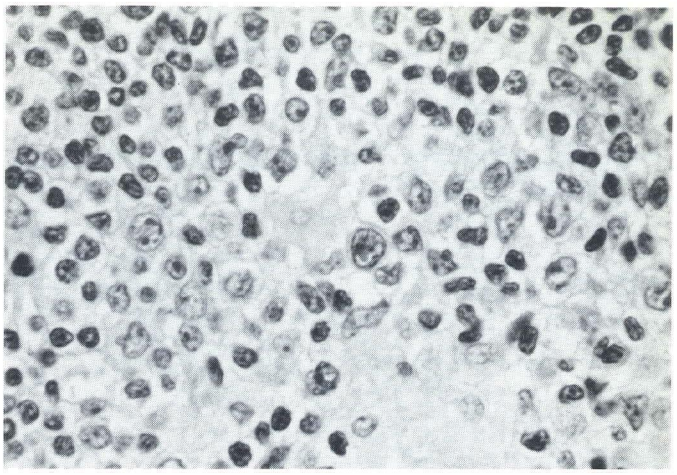

Fig 9 (case 3)—Malignant lymphoma diffuse mixed cellularity type involving the cervical lymph node (hematoxylin-eosin stain, X630).

The three patients presented here exhibited clinicopathologic features which are significantly different from the well-described cases of Richter's syndrome, LCL development in CLL, and acute lymphoblastic leukemia as a terminal phase in CLL. Grossly evident multifocal osteolytic LCL without organomegaly or lymphadenopathy in case 1, localized marrow LCL without soft tissue involvement in case 2, and the development of mixed lymphocytic-histiocytic lymphoma in case 3 are all very unusual. To our knowledge, osteolytic LCL occurring in CLL has not been reported. Furthermore, the development of mixed lymphoma in case 3 with extinction of CLL but with brisk favorable response to chemotherapy is of considerable interest and is very unusual. Finally, the presence of similar immunologic markers in the CLL cells and LCL cells in all three cases would suggest a transformation or dedifferentiation of the original neoplastic lymphoid clone rather than de novo appearance of another neoplasm.

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