Atypical Lymphoid Leukemia in Ataxia Telangiectasia

By Ralph Levitt, Robert V. Pierre, William L. White, and Robert G. Siekert

We observed two sisters with ataxia telangiectasia, one of whom developed an atypical subacute lymphocytic leukemia characterized by atypical lymphocytes and absence of palpable lymphadenopathy or hepatosplenomegaly. The lack of organomegaly in this patient may have been due to the underlying ataxia telangiectasia, which was associated with lymphoid hypoplasia. Cytogenetic studies showed a marker chromosome 14 [t(14q11:14q34)] in both patients. The sister with leukemia had other complex chromosomal aberrations in addition to the marker chromosome 14 that were stable for more than 14 mo before the patient's death from complicating infection. The development of atypical T cell leukemia has not been previously described in ataxia telangiectasia. This case further illustrates the interesting interrelationships among immunosuppressed states, development of lymphoid malignancy, and an emerging pattern of a propensity to chromosome 14 abnormalities in various lymphoid malignancies.

The interrelationship of cytogenetic aberrations and malignancy in ataxia telangiectasia has evoked considerable interest. We observed since their childhood two sisters with ataxia telangiectasia and recently performed cytogenetic studies on them. One sister suffered an atypical T cell lymphocytic leukemia, while the other remained free of hematologic disease. Both patients, however, had similar clonal cytogenetic abnormalities with rearrangement of chromosome 14, t(14q11:14q34). Abnormalities of chromosome 14 have been previously described in ataxia telangiectasia. The increased frequency of lymphocytic leukemia and lymphoma in patients with ataxia telangiectasia has been ascribed to the increase in spontaneous chromosomal breakage and clonal rearrangements in the setting of an impaired immunologic milieu. Only a few patients with ataxia telangiectasia who have these malignancies have been studied by cytogenetic techniques.

CASE REPORTS

The parents of our patients were nonrelated Caucasians of northern European ancestry. The parents had no neurologic or hematologic abnormalities, and there was no family history of ataxia telangiectasia. There were two siblings, 25-yr-old and 23-yr-old females, who had no clinical or neurologic features of ataxia telangiectasia and no immunologic or hematologic disorders.

Case 1. This patient was initially seen at the Mayo Clinic in 1949 at age 15 mo. Her childhood clinical and neurologic features were previously reported. At the age of 18 yr she had a normal complete blood count and peripheral blood smear.

On routine reexamination at the age of 25 yr (Nov. 11, 1975), she had a small stature and the hallmark signs of cerebellar ataxia and oculocutaneous telangiectasia. Electromyographic examination also confirmed evidence of distal motor and sensory neuropathy. Laboratory studies showed a serum IgA level of 0.15 mg/ml (normal 0.3-3.0) and an IgE level of 234 ng/ml (normal 6-780).
Case 1. Peripheral blood smear showing large, atypical, immature lymphocytes with prominent nucleoli and some nuclear folding. Wright stain. x 1000.

The hemoglobin level was 13.4 g/dl, leukocyte count 48,400/mm³, and platelet count 318,000/mm³. There were 73%, lymphocytes, many of which resembled large atypical lymphocytes. Many of the cells had prominent nucleoli and resembled prolymphocytes (Fig. 1). Results of monospot and heterophil tests were negative. Cell marker studies showed that of peripheral blood lymphocytes 58%, were T cells and 11%, were B cells. Bone marrow examination showed that 30%, of nucleated cells were large atypical lymphocytes similar to those observed in the peripheral blood. A diagnosis of atypical subacute lymphocytic leukemia was made; however, because of the lack of symptoms, specific therapy was not instituted.

Twelve months later (Nov. 23, 1976) the patient returned with a history of increasing fatigability of 2 mo duration. There was still no organomegaly. The hemoglobin level was 10.9 g/dl, the leukocyte count 613,000/mm³ with 95%, large atypical lymphocytes, and the platelet count 52,000/mm³. The bone marrow was virtually replaced by lymphocytes. Therapy was begun with chlorambucil 8 mg and prednisone 40 mg. Six weeks later the leukocyte count had decreased to 170,000/mm³. During the eighth week of therapy, the patient experienced fever, increasing dyspnea, and cough. A chest roentgenogram showed a diffuse interstitial infiltrate. Respiratory failure rapidly developed, and the patient died.

Autopsy revealed bronchopneumonia due to Pneumocystis carinii and Candida albicans. Although there was leukemic tissue infiltration on microscopic examination, the lymphoid tissue was generally hypoplastic. The spleen weighed 195 g; the liver weighed 995 g. The neurologic findings included diffuse cerebellar cortical atrophy, degeneration of the posterior spinal cord columns, and multiple capillary telangiectasia of the cerebral white matter. Bizarre large nuclei were seen in the spinal posterior ganglion capsular cells.

Case 2. The younger sister of patient 1 was first seen at the Mayo Clinic in 1952 at the age of 3 yr. At the age of 21 yr she had a small stature and typical signs of ataxia telangiectasia. She also had low levels of serum IgA and abnormalities on electromyographic studies. Her hematologic findings were entirely normal. She remained essentially unchanged on subsequent examinations, with the most recent examination in November 1977 at the age of 24 yr.
MATERIALS AND METHODS

Unstimulated lymphocyte cultures were obtained from heparinized peripheral blood of case 1. Incubation was carried out for 24 or 48 hr in culture medium containing fetal calf serum 20%, Eagle Minimum Essential Medium (MEM), penicillin, and streptomycin. Colchicine was added during the last 4 hr of culture. Chromosome preparations were made using the modified Tjio-Whang method. Direct bone marrow chromosome analyses were performed by the Lam-Po-Tang modification. Stimulated peripheral blood lymphocyte cultures were done by the Difco TC Chromosome Culture Kit (Difco, Detroit, Mich.). Giemsa banding was done using a modification of the method of Patil et al. R, C, and Q banding studies were done by reported methods. T and B lymphocyte cell marker studies were performed by standard methods. Mitotic index was determined on Carnoy fixed cell suspensions by counting 5000 cell nuclei and determining the percentage that contained mitotic figures. Karyotypes were arranged according to the recommendation of the Paris Conference on Human Cytogenetics.

RESULTS

The results in case 1 show the following notable features (Table 1): The initial direct bone marrow study (Nov. 11, 1975) showed no abnormality. This result was surprising in view of the extent of the leukemic involvement; however, the low mitotic index of the tumor cells, as demonstrated on the direct preparations of the peripheral blood on Nov. 23, 1976, undoubtedly explains the finding. In contrast, 72-hr phytohemagglutinin (PHA)-stimulated cultures of the peripheral blood leukocytes showed abundant growth of the leukemic cells, as identified by the presence of a clonal aneuploid karyotype, whereas unstimulated cultures of the peripheral blood leukocytes showed very sparse growth. The culture pattern observed in this patient was the opposite of that usually observed in patients with acute leukemia in whom growth in unstimulated cultures occurs without growth of leukemic cells in PHA-stimulated cultures. The leukemic cells showed a normal pattern of T cell PHA respon-

<table>
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<th>Date</th>
<th>Type of Study*</th>
<th>Total No. of Cell Studies</th>
<th>Modal No.</th>
<th>Mitotic Index†</th>
<th>Results</th>
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<td>0.18</td>
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<td>43</td>
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<td>17, all abnormal‡</td>
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<td>No metaphase found</td>
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<td>43</td>
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<td>8, all abnormal§</td>
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<tr>
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<td>13</td>
<td>45</td>
<td></td>
<td>12-45,XX, t(14q11:14q34)</td>
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*BM, bone marrow; PB, peripheral blood; UNS, unstimulated culture; PHA, phytohemagglutinin-stimulated culture; 24, 48, 72, hours of culture; G, Giemsa stain; GB, Giemsa banding; C, C banding; R, R banding; Q, Q banding.
†Mitotic index was determined by counting number of mitotic figures per 5000 cell nuclei.
‡Metaphases with complex rearrangements. Only incomplete description was possible from the banding studies; however, they were stable rearrangements and similar in all studies. Each metaphase contained a t(14q11:14q34); t(13:15); t(13:17); an 18q+ marker; and three small markers.
siveness; no metaphases were observed in cultures harvested at 24 or 48 hr, whereas abundant metaphases were present at 72 hr. This is in contrast to the delayed PHA response in typical chronic lymphocytic leukemia and previously described in ataxia telangiectasia.

The marker chromosome observed in these patients was a tandem translocation of chromosome 14, depicted as an ideogram in Fig. 2. The identity of the involved chromosome was confirmed with Q and R banding studies. C banding studies showed a small amount of centromeric heterochromatin at the attachment site (Fig. 2). Some metaphases had slight constrictions at that area, suggesting a dicentric chromosome. The loss of material from the two chromosomes 14 in these patients was minute, consisting only of the telomeric end of one chromosome 14 and a portion of the centromere and satellite region of the homologue.

Patient 1 had additional complex rearrangements (Fig. 3). The rearrangements could not be fully elucidated; three small marker chromosomes could not be identified. There were, however, consistent abnormalities in addition to the t(14q11:14q34). Each metaphase contained translocation chromosomes t(13:15) and t(13:17) and an 18q+ marker. One normal homologue of chromosomes 15, 16, 21, and 22 was observed; the other homologue was involved in marker chromosome formation. All members of chromosome groups A, B, and X appeared to be normal in all metaphases. No consistent C-group abnormalities were found.

The chromosome abnormalities in case 2 were limited to the t(14q11:14q34)
marker in 72-hr PHA-stimulated peripheral blood culture studies utilizing Giemsa banding (Fig. 4). PHA-stimulated 72-hr peripheral leukocyte cultures of the parents and two siblings who did not have ataxia telangiectasia showed no significant chromosome abnormalities by G banding.

DISCUSSION

We described patient 1 as having an atypical subacute lymphocytic leukemia because of the morphologic and clinical features. Although the fairly rapid
progression of the disease process during a period of 1 yr suggests an acute process, she was essentially asymptomatic during most of this time. The lymphocytes were not blastic in their structure. Most cells resembled large atypical lymphocytes, such as are seen in viral infections, and others suggested prolymphocytes (Fig. 1). The disease was considered to be a T cell process on the basis of the following evidence: the tumor cells were responsive to PHA in the usual pattern, most of the cells in the peripheral blood were typed as T lymphocytes, and the cytogenetic studies suggested that the leukemic cells had their origin in
the patient's preexisting ataxia telangiectasia lymphocyte clone. The evidence for T cell origin of the leukemia in this case is inferential but convincing. There are similarities in the leukemia observed in this patient with the T cell prolymphocytic leukemia described by Catovsky et al. They defined this entity as a subacute leukemia with high lymphocyte counts of the prolymphocyte variety, gross splenomegaly, little adenopathy, and poor response to therapy. The full expression of this disorder may have been attenuated or modified in our patient by the association of ataxia telangiectasia and hypoplasia of lymphoid tissue.

Brouet et al. described 11 patients with T cell chronic lymphocytic leukemia. In two of their patients, the disease features resembled those in our leukemic subject. There was a severe leukocytosis due to prolymphocytes and extensive bone marrow replacement. Our patient differed by having a more aggressive course of her disease. Nowell et al. also described a patient with chronic lymphocytic leukemia of T cell type. The lymphocytes in their patient were described as predominantly mature cells. The patient had a pronounced elevation of the leukocyte count, extensive lymphadenopathy, and greatly enlarged liver and spleen.

Our patient did not have a mediastinal tumor mass, which is often associated with acute lymphoblastic leukemia of T cell type, or skin involvement, which is the hallmark of T cell disorders such as Sézary syndrome or mycosis fungoides.

The cytogenetic studies on this family were consistent with the previous literature reports on ataxia telangiectasia. A marker chromosome 14 has been described as the characteristic finding in ataxia telangiectasia. The marker chromosome appears to be limited to a clone of lymphocytes. In our case 1, cells of myeloid origin did not contain the marker chromosome. The marker chromosomes 14 described in previous case reports of ataxia telangiectasia have been of two types: (1) a t(14q12:14q32) or a chromosome 14 with a breakpoint at 14q12 and translocation of the 14q arms to another chromosome, such as a chromosome 7 or X, or (2) a residual deleted chromosome 14. Case 5 in the report of McCaw et al. appeared to have a rearrangement in chromosome 14 similar to what was observed in our two patients except that the breakpoint in our patients' 14q was at or near the centromere (Fig. 2). The patient described by McCaw et al. had chronic lymphocytic leukemia and had additional cytogenetic aberrations affecting chromosomes 13, 15, 16, and 18, also observed in our case 1. In our cases, the break point on 14q and the telomeric end of the homologue 14 would result in a very small deleted 14. A deleted 14 was not identifiable in our cases but could be represented by one of the small unidentifiable marker chromosomes present in case 1; however, in case 2, in which only the marker chromosome 14 was present, no extra small chromosome was demonstrable. These findings suggest to us that the residual deleted chromosome 14 and the telomeric end of the homologue either were lost or formed small unrecognizable translocations to other chromosomes.

The presence of the t(14q11:14q34) marker in the leukemic cells of patient 1, identical to the marker chromosome in her sibling with ataxia telangiectasia, strongly supports the contention that her leukemic cell line arose from the ataxia telangiectasia lymphoid cell type. Case 5 of McCaw et al. had the docu-
mented presence of the same marker chromosome 14 in her preleukemic ataxia telangiectasia cell line as well as in her leukemic cells, and this led them to suggest that the leukemia had developed from the preexisting ataxia telangiectasia cell line.

Ataxia telangiectasia appears to be characterized by a clone of lymphocytes that exhibits an increase in spontaneous chromosomal breakage in cell cultures. More recent cytogenetic studies suggest that the ataxia telangiectasia lymphocyte clone typically contains a rearrangement of the 14q arms. Patients with ataxia telangiectasia have an unusually high incidence of secondary lymphoid malignancies (10% overall) as well as nonlymphoid malignancies. There is also a fivefold higher than expected incidence of lymphoma, leukemia, and biliary, gastric, and ovarian malignancies in heterozygous relatives of patients with ataxia telangiectasia. It is speculation at this time to assume that the presence of an abnormal lymphocyte clone, depressed cellular immunity, susceptibility to chromosome breakage, or a relatively specific chromosomal rearrangement is responsible for the increased incidence of malignancy in patients with ataxia telangiectasia and carriers of ataxia telangiectasia; however, it is difficult to avoid such a conclusion. Such speculation that the rearrangements of chromosome 14 are the cause or reflect the effect of a process responsible for the development of neoplasia is supported by the observations that similar abnormalities of chromosome 14 are being found with various lymphoid neoplasms. Abnormalities of chromosome 14 have been described in Burkitt lymphoma, Hodgkin disease, malignant lymphoma (lymphocytic and histiocytic types), and plasmacytic myeloma. To date, the 14q+ abnormality has not been reported as a frequent or characteristic finding in acute lymphocytic leukemia or T cell leukemias such as Sézary syndrome. Whether or not current interest in the 14q+ abnormality will stimulate the search for and recognition of this abnormality in acute lymphocytic leukemia and other T cell disorders is unknown.

Our findings add further support to the specificity of 14q rearrangements to lymphoid malignancies. Future studies may elucidate the role of 14q as a leader (causative) or as a follower (a malignancy-induced change).

REFERENCES

9. Lam-Po-Tang PRLC: An improved
32. Mark E, Histiocytic lymphomas with the marker chromosome 14q+. Hereditas 81:289, 1975
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