Burkitt’s Lymphoma in AIDS: Cytogenetic Study

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Cytogenetic studies were done in two cases of Burkitt’s lymphoma in homosexual individuals with possible acquired immune deficiency syndrome (AIDS). The chromosomal abnormalities found are consistent with those previously described in the nonendemic form of Burkitt’s lymphoma, with one of the two patients having the variant translocation, t(8;22). The production of the kappa light chain immunoglobulin by the tumor cells from the patient having t(8;22) and the occurrence of the different sites of translocation of the duplication of 1q in the second patient are unusual findings. Whether there is an increase in the incidence of the variant translocation t(8;22) is yet to be determined.

In May 1982, Doll and List1 reported the first case of undifferentiated lymphoma resembling, or identical to, Burkitt’s lymphoma in a male homosexual who also had Giardia lamblia colitis and rectal gonorrhea. Ziegler et al.,2 while investigating Kaposi’s sarcoma in the homosexual population in the San Francisco Bay area, noted four men with Burkitt-like lymphoma and suggested that there was an outbreak of this neoplasm in homosexual men. These reports prompted us to describe the cytogenetic studies in two cases of Burkitt’s lymphoma in one homosexual man and one bisexual man with probable acquired immune deficiency syndrome (AIDS). It is hoped that these chromosome analyses may help to provide some insight into the nature of AIDS and its relationship to Burkitt-like lymphomas.

MATERIALS AND METHODS

Patients

Both cases of probable AIDS associated with Burkitt’s lymphoma were admitted to the Clinical Center, National Institutes of Health, Bethesda, MD, for evaluation and treatment.

Patient 1 was a 30-yr-old white male homosexual with a history of fatigue and weight loss over the previous 4 mo. When first seen, he had an advanced, widespread neoplasm involving bone marrow, peripheral blood, liver, spleen, peripheral lymph nodes, pleurae, and the central nervous system. Burkitt’s lymphoma was confirmed cytologically and histologically. In addition, ulcerating lesions caused by Herpes simplex virus (confirmed by culture) were seen on the buttocks. Hepatitis B core and surface antigens were positive, and there were elevated antibody titers against Epstein-Barr virus (EBV) antigens [viral capsid antigen (VCA) 1:1280; early antigen (EA) 1:80; and EBV nuclear antigen (EBNA) 1:20], as well as an increased antibody titer against cytomegalovirus (CMV) [1:128 (normal <1:32)]. CMV was cultured from the blood and urine as well as from lung tissue obtained postmortem. The lactate dehydrogenase (LDH) was 420 U/liter (normal 15-340 U/liter). The tumor cells were positive for EBNA; and there was an inverted ratio between OKT4 (helper) and OKT8 (suppressor) peripheral T lymphocytes (0.4, normal >1.6). Bone marrow and pleural fluid were obtained for cytogenetic studies prior to chemotherapy on June 22, 1982. Chemotherapy was initiated with marked improvement, but the patient developed a profuse demyelinating syndrome and died from intracerebral hemorrhage after 3 cycles of therapy.

Patient 2 was a 23-yr-old white male who presented with increasing abdominal girth of 9 days duration. He had been bisexual for 6 yr, with a different sexual partner every 3 wk. He used amyl nitrate for an 8-mo period 1 yr ago. Physical exam and staging studies revealed a pelvic mass in the region of the prostate, ascites, and bilateral pleural effusions. A diagnosis of Burkitt’s lymphoma was made on a biopsy of the rectal mass; both pleural fluid and ascites contained malignant cells. Cerebral spinal fluid (CSF) and bone marrow were normal. The LDH was 1,070 U/liter. Hepatitis A antibody titer was positive and hepatitis B negative. EBV antibody titers were increased (VCA, 1:2560; EA, 1:80, and EBNA, 1:80). The CMV titer was 1:32, and the throat and urine cultures for the virus were negative. The tumor cells were EBNA positive, and the ascitic fluid and throat cultures were positive for EBV. The ratio of OKT4 to OKT8 T-lymphocytes was 0.8. Ascites and pleural fluid were obtained for cytogenetic studies on February 23, 1983. Chemotherapy was begun with cyclophosphamide; this was followed by severe, acute tumor lysis, necessitating hemodialysis. Bilateral pulmonary infiltrates, believed to represent Pneumocystis carinii pneumonia, developed, although a transbronchial biopsy failed to reveal a pathogen. The patient required mechanical ventilation but improved after treatment with Bactrin. He achieved complete remission, and has remained in complete remission with continued chemotherapy for 4 mo.

Chromosome Analysis

Direct, air-dried chromosome preparations were made from the bone marrow, ascites, and pleural fluid according to the technique of Tjio and Whang.3 In addition, each specimen was cultured for 1–4 days in RPMI 1640 medium supplemented with penicillin, streptomycin, glutamine, and 20% fetal calf serum. These cultures were harvested according to a modification of the method of Moorhead et al.4 One slide from each specimen was stained with conventional Giemsa and the remainder were G-banded using trypsin-Giemsa.5 Metaphases were scored for aberrations, and karyotypes were prepared according to the Paris Conference.6

RESULTS

Case 1

Detailed chromosome analyses are presented in Table 1. Both the direct and 1-day culture of the bone marrow had a modal number of 46; G-band analysis showed that 14% of the cells had a karyotype of 46,XY,t(8;22)(q24;q12); 64% of the cells, in addi-
tion to t(8;22), had a duplication of a region of the long arm of chromosome 1, i.e., a karyotype of 46,XY,dup1(q21-32),t(8;22); and 22% of the cells had a double duplication of 1q21-32 on chromosome 1.

Analysis of the direct preparation of the pleural fluid also showed a modal number of 46 and the abnormality of chromosome 1, as well as t(8;22). G-banding analyses revealed 75% of the metaphases to have a karyotype of 46,XY,dup1(q21-32),t(8;22) and 25% to have a double duplication of 1q along with t(8;22) (Figs. 1 and 2).

Case 2

The details of the cytogenetic analysis of the two fluids from different sites obtained on the same day are listed in Table I. The chromosome number of the short-term culture of the ascites ranged from 44 to 47, with the hypodiploid cells showing random loss. Four of the cells (5%) had a normal male karyotype, 46,XY. All of the remaining cells (96%) had the typical 8;14 translocation, as well as a duplication of the 1q21-32 region or of the 1q21-44 region. In 18% of the cells, there was a duplication of 1q21-32 that remained on chromosome 1. The remainder of the abnormal metaphases (77% of the cells) had a duplication of the 1q21-44 region. In 71% of the metaphases, this part of chromosome 1 translocated to the long arm of chromosome 4; in 6%, it translocated to the long arm of chromosome 19.

Cytogenetic analysis of the pleural fluid showed 5 cells with 45 chromosomes (random loss), 34 cells with 46 chromosomes, and 1 cell with 47 chromosomes. In all of the cells, there was t(8;14), and the duplicated portion of 1q21-44 was translocated to the long arm of chromosome 4. There was no increase in breaks or aberrations seen in these samples (Figs. 3 and 4).

DISCUSSION

Recently, an increase in patients with Burkitt-like lymphoma associated with acquired immune deficiency syndrome (AIDS) has been noted.1,2,7 This acquired T cell immunodeficiency syndrome has generally been associated with invasive Kaposi’s sarcoma and opportunistic infections and has been described in homosexual men, intravenous drug abusers, patients with hemophilia, heterosexual Haitian refugees with no history of intravenous drug abuse, and prisoners.8-19

Cytogenetic analyses of two cases of Burkitt-like lymphoma in association with AIDS have recently been reported.7 One patient’s tumor had t(8;14) and the second had t(8;22) in addition to 9q-. In previously reported cases of endemic and nonendemic Burkitt’s lymphoma, the most frequent chromosomal abnormality was t(8;14)(q24;q32), with t(2;8)(p12;q24) and t(8;22)(q24;q11 or q12) being found less often.20-24 Our two cases, along with those of Chaganti, demonstrate 2 patients with t(8;14)(q24;q32) and 2 patients with t(8;22)(q24;q11 or q12). This finding may indicate an increase in the frequency of t(8;22) in these patients, although many
more cases are needed to ascertain the true incidence of this variant.

An interesting finding in our two patients is the duplication of 1q21-32 or 1q21-44. The translocation of the duplicated portion of 1q to several different chromosomes, found in metaphases of the same specimen, has not previously been reported, although the double duplication has been previously described by Douglass et al.22 and others23 in nonendemic Burkitt’s lymphoma. In addition to t(8;14), 10 of Douglass’ 18 patients had a peculiar marker chromosome 1 that had a duplication of bands q12-31 or q21-31, either once or twice. Abnormalities of chromosome 1 have been reported in many hematologic malignancies,24 including myeloproliferative disorders25 and Burkitt’s lymphoma,2223 as well as in carcinoma of the breast,27 cervix,28 lung,29 ovary,30 and in malignant melanoma.31 These abnormalities include reduplication, trisomies, rearrangements, and isochromosomes, almost always involving the 1q21-25 or 1q25-32 region. The mechanism of the duplication of a chromosomal region is not known. The relationship between the existence of this duplicated segment (either once or twice), its translocation to other chromosomes, and the development of neoplastic diseases remains to be investigated. To date, one transforming oncogene, a new member of the ras gene family (N-ras), has been identified in two human sarcoma cell lines and has been assigned to chromosome 1. The exact region of the chromosome has not yet been determined.32 The relationship between this gene and region 1q21-25 or 1q25-32 may provide an explanation for the activation of this cellular oncogene.

Chromosome translocations typical for Burkitt’s lymphoma involve chromosome 8, as a recipient and/or donor chromosome, for chromosomes 2, 14, and 22. The genes for the immunoglobulin heavy chains have been assigned to chromosome 14, band q32.3,33 the genes for kappa light chains to 2p12,34 and the genes for the lambda light chains to 22q12.35 Studies on the nature of the heavy and light chain surface immunoglobulins synthesized by Burkitt’s tumor cells with variant translocations, especially t(2;8) and t(8;22),

![Figure 3](image-url)
have been extensively reviewed by Abe et al. The light chains produced by cells with t(8;14) have been either lambda or kappa; cells with t(2;8) have produced kappa light chains in 3 of 7 cases (in 2 cases light chains could not be detected), and cells with t(8;22) have produced only lambda light chains in 9 of 10 cases studied (in 1 case, light chains were not detectable). These investigators postulated that when the gene(s) from chromosomes 2 or 22 are translocated to chromosome 8, they might be activated at this new locus and exclusively produce the light chain immunoglobulins coded for at the gene loci on these chromosomes. Cell lines established by Magrath et al. from bone marrow, peripheral blood, and pleural fluid from case 1 retained the chromosomal abnormalities of t(8;22) and the duplication of 1q. These lines, like the original tumor cells, were shown to synthesize the kappa light chain rather than the anticipated lambda light chain type. Additional tumors and cell lines with all the various translocations found in Burkitt’s lymphoma, including t(8;22), must be examined carefully for the range of genetic rearrangements and their consequences at the molecular level.

Recent advances in techniques for in situ hybridization of radioactively labeled DNA probes have made it possible to map cellular oncogenes to specific chromosomes. The c-myc oncogene has been shown to be on chromosome 8 at the breakpoint commonly involved in Burkitt’s lymphoma, band q24. In the two patients of the present study, the translocations involving chromosomes 8 and 22 or 8 and 14 may have resulted in activation of this oncogene and may have led to malignant transformation, with clonal proliferation of the neoplastic cells resulting in Burkitt’s lymphoma. More studies of tumors and cell lines having variant translocations, using the techniques of in situ hybridization and blot analysis with cloned molecular probes, are required.

ACKNOWLEDGMENT
The authors would like to thank Drs. Susan Bates, Marcia Brown, and Harry Masur for providing the clinical information for these patients, and Gary Armstrong for the virology studies.

REFERENCES


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