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Clinical Notes

Acute Leukemia With Ph¹-Like Chromosome in an LSD User

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Acute leukemia occurred in a user of several hallucinogenic drugs (lysergic acid diethylamide [LSD], mescaline, marihuana, and amphetamines). The leukemic leukocytes of the patient contained a Ph¹-like chromosome; lymphocytes transformed with phytohemagglutinin did not show chromosome breaks. A Ph¹-like chromosome has only rarely been reported in either acute leukemia or in cultured lymphocytes of individuals ingesting LSD.

RECENT REPORTS have shown that lysergic acid diethylamide (LSD) can cause chromosomal abnormalities[1-3] including the presence of a chromosome anomaly morphologically similar to the Philadelphia chromosome (Ph¹).[1,3] The presence of these chromosomal aberrations has led to speculation regarding the possible increase in the incidence of leukemia in users of LSD.[2,3] To our knowledge, this is the first reported case of acute leukemia following LSD ingestion, and it is of further interest since the leukocytes in this patient contain a Ph¹-like chromosome similar to those commonly associated with chronic myelocytic leukemia (CML)[4,5] but only rarely with acute myelocytic leukemia.[5-10]

Report of a Case

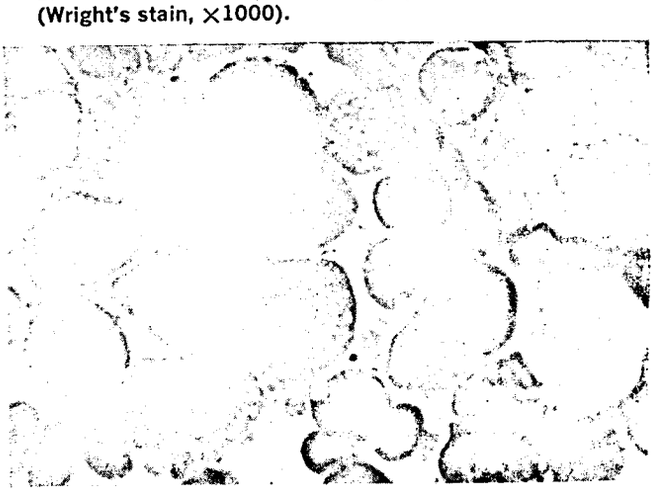
The patient (PH#188-08-63), a 19-year-old college freshman, was admitted to the Presbyterian Hospital for the first time on Dec 28, 1967 with a chief complaint of fever and malaise of ten days' duration.

The family history revealed that the patient's maternal grandmother, mother, three siblings (one brother and two sisters), and one female first cousin had all had splenectomies for hereditary spherocytosis. The disease has also been documented as having occurred in two maternal uncles and one female first cousin.

The patient alleges having taken 15 doses of LSD ranging from 100 to 250μg during the period between October 1966 and August 1967. During the year prior to admission he had also used mescaline on four occasions as well as marihuana and amphetamines. He had no medical history of chemical or radiation exposure and had not received other medications.

The patient was well until one month prior to admission when he noted easy fatigability and pallor. Two weeks prior to admission intermittent fever to 102 F (38.9 C) developed along with cough, sweats, nonpleuritic chest pain, and generalized abdominal pain mainly in the left upper quadrant. There was no bleeding in the gums, bruising, or petechiae. On admission, his temperature was 102 F rectally. Pertinent positive physical findings included pallor, a flame-shaped hemorrhage in the fundus of the right eye, splenomegaly to 8 cm below the left costal margin, and hepatomegaly to 3 cm below the right costal margin. Laboratory studies revealed the following values: hemoglobin, 12 gm/100 cc; white blood cell count (WBC), 62,000/cu mm, with 38% blast forms, 11% myelocytes, 16% metamyelocytes, 17% band forms, 9% neutrophils, and 9% lymphocytes. One nucleated red blood cell (RBC) was present per 100 WBC. The peripheral blood cell smear showed slight to moderate anisocytosis with some spherocytes. The platelet count was 53,000/cu mm. The bone marrow was hypercellular and showed more than 90% blast cells in clumps and sheets, many containing vacuolated cytoplasm (Fig 1). Uric acid concentration was 12.6 mg/100 cc; prothrombin time, 18 seconds (control, 13 seconds); serum glutamic oxaloacetic transaminase (SGOT), 72 units; alkaline phosphatase level, 18 King-Armstrong units; and leukocyte alkaline phosphatase value was 4 (control, 10 to 70). The osmotic fragility of the patient's RBC was increased with hemolysis starting at 0.55% saline and ending at 0.4% (control, 0.45% and 0.3%, respectively), which is consistent with a diagnosis of hereditary spherocytosis. Multiple blood cultures and nose, throat, urine, and stool cultures showed no growth. Reticulocyte count, and serum bilirubin and cyanocobalamin levels were within normal limits. The patient was treated with a high-fluid regimen, prednisone (150 mg daily), and allopurinol (300 mg daily), and responded with prompt lysis of fever, subsidence of symptoms, and regression of hepatosplenomegaly. The WBC fell to 10,800/cu mm by the seventh day of therapy with a normal differential cell count, while the platelet count rose to 110,000/cu mm. However, repeated bone-marrow aspiration showed decreased cellularity with 15% to 20% blasts. One month later, his WBC again rose to 47,600/cu mm, with 5% blasts, 4% bands, 46% mature neutrophils, and 20% lymphocytes. He was therefore readmitted in February 1968 and was treated with a ten-day course of mercaptopurine (50 mg daily), prednisone (80 mg daily), and vincristine sulfate (3.25 mg intravenously on the first and fourth days). During the course of this therapy his hepatosplenomegaly disappeared, peripheral WBC fell to 6,000/cu mm, with a normal differential cell count. His platelet count rose to 250,000/cu mm, and a repeated bone-marrow aspiration revealed no abnormalities. Therapy was maintained with methotrexate (20 to 30 mg orally, twice weekly) and was continued with allopurinol.

1. Bone marrow photomicrograph on admission (Wright's stain, ×1000).



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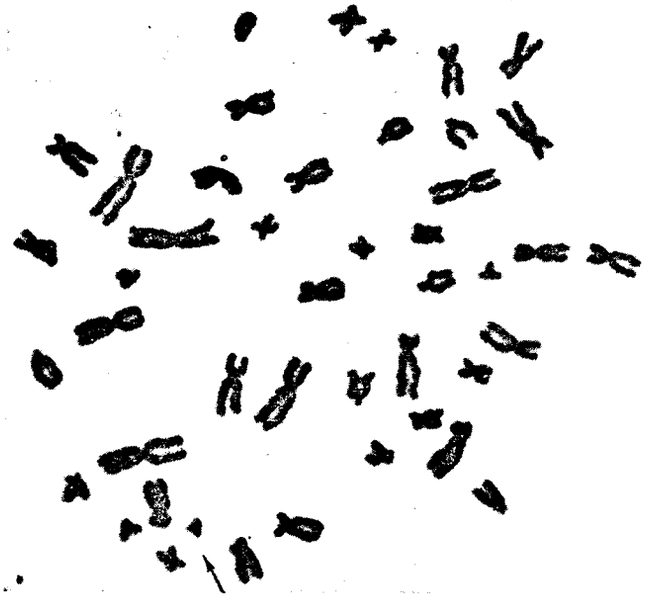

2. Metaphase in peripheral blood cell after 24 hours incubation without phytohemagglutinin. *Arrow* denotes Ph¹-like chromosome.

His symptoms remained in complete remission until April 20, when he was readmitted to the Medical Service with a two-day history of malaise and temperature of 104 F (40 C). Physical examination again revealed hepatosplenomegaly. The hemoglobin value was 14 gm/100 cc and the WBC was 50,000/cu mm, with 5% blasts, 2% myelocytes, and 2% metamyelocytes. An occasional nucleated RBC was seen on smear. Platelet count was 214,000/cu mm and bone-marrow aspiration showed 14% blasts. The patient received a second course of therapy with mercaptopurine, prednisone, and vincristine, as described previously, and responded with a lysis of his fever, a decrease in his peripheral WBC to 10,000/cu mm, with a normal differential cell count and a return of his marrow blast percentage to normal. The hemoglobin value and platelet count remained normal. He was discharged on a maintenance regimen of mercaptopurine (25 to 50 mg daily) and allopurinol.

A study of the patient's chromosomes in peripheral blood cells was performed prior to chemotherapy with the methods described previously.[11] All 35 of his metaphase cells after 24 hours of culture without phytohemagglutinin (PHA) showed a Ph¹-like chromosome (Fig 2). After 72 hours of culture with PHA, only a few of the cells in metaphase showed the Ph¹-like chromosome. Fifty normal cells from the latter culture were examined for the presence of chromatid or isochromatid breaks, dicentric or other reunion figures, or altered count distribution. None of these were found except for one chromatid break which was no different from the control frequency of 3% usually seen in our laboratory. No endoreduplicated cells were seen. Examination of the patient's father's chromosomes in peripheral blood cells showed no abnormalities. We have not been able to obtain the mother's cells for study.

Comment

Several factors favor the diagnosis of acute myelocytic leukemia in this patient: (1) the age of the patient and the rather abrupt onset of the illness with lack of any preceding symptoms suggestive of preceding chronic leukemia; (2) the hematologic picture with a uniform cell type in a hypercellular marrow (more than 90% blasts) associated with an abnormal stem-cell population in the periphery; (3) the persistent absence of basophilia both during exacerbation and remission; and (4) the good (though partial) clinical and hematological remission following therapy with prednisone alone. The diagnosis of a blastic crisis of CML cannot be excluded although the patient's favorable response to prednisone therapy as well as the other factors cited previously are against this possibility.[12]

Recent studies[1,3] have demonstrated that LSD (both in vitro and in vivo) has been associated with chromosomal abnormalities in cells cultured in vitro. These abnormalities in LSD users include rates of chromosomal breakage that are two to six times as great as those observed in controls, structural chromosomal rearrangements (particularly dicentric chromosomes and exchange figures) that are absent in controls, and rarely, the presence of a Ph¹-like chromosome.[1,3] It has been suggested that one of the obvious potential dangers of exposure to agents such as LSD is a possible future increase in the incidence of leukemia and other neoplasms in exposed persons.[2,3]

The association of LSD ingestion with the subsequent occurrence of acute leukemia in the case reported here is, therefore, of great interest, although a causal relationship of LSD to acute leukemia remains to be established. The relation of LSD ingestion to the presence of a Ph¹-like chromosome in this case must also remain speculative, especially in view of the absence of chromosome breaks in PHA-stimulated cells of the lymphoid series. A chromosomal abnormality morphologically indistinguishable from the Ph¹ chromosome has been reported previously following LSD ingestion.[1,3] However, a similar chromosomal defect, although most often associated with CML, has also been reported, although only rarely, in other conditions diagnosed as acute leukemia,[5-10] myeloid metaplasia,[13,14] polycythemia vera,[15] atypical myeloproliferative syndrome with marked thrombocytosis,[16] eosinophilic leukemia,[17] and in apparently healthy descendants of patients with CML.[18] Only further reports on the development of the Ph¹ chromosome or leukemia or both in LSD users can accurately define the relationship between these entities and the ingestion of the drug.

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Generic and Trade Names of Drugs

Prednisone—*Cotone, Delta-Dome, Deltasone, Deltra, Lisacort, Metasone, Meticorten, Paracort.*
Allopurinol—*Zyloprim.*
Mercaptopurine—*Purinethol.*
Vincristine sulfate—*Oncovin.*

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Unsuspected Infectious Hepatitis in Surgical Patients

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Clinical, laboratory, and histologic abnormalities of hepatic injury attributed to the use of halothane are almost indistinguishable from those caused by viral hepatitis. In three patients upon whom emergency surgery was performed, infectious hepatitis was detected from laboratory data or liver biopsy before the disease became clinically evident. Preoperatively, hepatitis was not suspected from the history or physical examination. Since infectious hepatitis may flare up following surgery and anesthesia, a high degree of suspicion should be standard.

THE RELATIONSHIP of hepatic injury to the newer halogenated anesthetics, ie, halothane (Fluothane) and methoxyflurane (Penthrane), remains unresolved despite numerous investigations.[1-6] Liver function and enzyme studies revealed no significant differences in patients receiving halothane or nonhalogenated agents.[3,4] Reviews of hospital or autopsy records or both failed to demonstrate any definitive association between liver complications and specific anesthetic agents.[5,6] The National Halothane Study,[2] a retrospective investigation of 856,500 instances of general anesthesia administration at 34 hospitals, found that most cases of postoperative massive necrosis of the liver were attributable to shock, overwhelming infection, or preexisting liver disease. In only nine cases was there no clear explanation for the liver injury. Of the patients in these cases, seven had received halothane, one cyclopropane, and one ethylene. However, isolated cases of hepatic dysfunction or necrosis continue to be reported, particularly following repeated administration of halothane.[7,8]

Clinical, laboratory, and histologic abnormalities attributed to halothane are almost indistinguishable from those caused by viral hepatitis.[9] Characteristically, malaise, transient fever, leukocytosis, anorexia, and vomiting occur two to six days after administration of anesthesia, while jaundice does not usually appear until after six to ten days. The delayed onset and low incidence with apparently increased occurrence and severity of the syndrome following repeated halothane administrations suggested a hypersensitivity reaction.[10]

The presence of infectious hepatitis at the time of operation with development of increased virulence secondary to the stresses of surgery and anesthesia, although a recognized possibility,[11,12] has not been emphasized. At the Albert Einstein College of Medicine, emergency surgery was performed in 1967 on three patients in whom infectious hepatitis was detected from laboratory data or liver biopsy when there was no suspicion of the disease from the history or physical examination. Investigation during the postoperative period revealed no history of liver disease, transfusions, medications, or contact with hepatic toxins or persons known to have hepatitis.

Report of Cases

CASE 1.—A 27-year-old woman was admitted at 39 weeks of pregnancy for a repeat cesarean section. History and physical examination were reported to indicate no abnormalities. Temperature was 97.7 F (36.5 C); blood pressure, 112/70 mm Hg; hematocrit value, 37%; and white blood cell count (WBC), 9,000/cu mm. Chemical profile revealed normal values except for the following: total bilirubin, 0.9 mg/100 cc; alkaline phosphatase, 18 King-Armstrong units; and serum glutamic oxaloacetic transaminase (SGOT), 384 units. Urine reaction was negative for protein, bilirubin, glucose, and acetone. The SGOT value indicated possible low-grade hepatitis. Therefore, a repeated chemical profile was done on the following day and it showed the following values: total bilirubin, 1.2 mg/100 cc; alkaline phosphatase, 19 King-Armstrong units; SGOT, 354 units; and serum glutamic pyruvic transaminase (SGPT), 590 units. A diagnosis of anicteric hepatitis was made on the basis of the elevated transaminase levels. Since the uterus was irritable, delivery could not be postponed, and cesarean section was performed with the pa-

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