Leukemia and Exposure to X-Ray: A Report of 6 Cases

By William C. Moloney

The leukemogenic effect of ionizing radiation in humans has been firmly established by studies of Japanese atomic bomb survivors and in a large series of spondylitis cases treated with x-ray. In these groups, because of the numbers of individuals involved and the circumstances of the radiation exposure, the leukemogenic effect of radiation can be accepted on statistical grounds. However, the etiologic role of x-ray or radioactive substances in the individual case of leukemia is difficult to evaluate. In the past year six patients have been encountered with leukemia and a history of relatively heavy exposure to x-ray. In this paper, these cases are briefly described, and some of the problems involved in establishing a diagnosis of radiation-induced leukemia are discussed.

Report of Cases

Case 1.—R.L., a 49 year old male, had a malignant testicular tumor removed in 1951. The patient refused radical lymph node dissection and was given x-ray therapy over the thoracic and abdominal paravertebral regions. Treatment consisted of 2800 r (in air) with 250 Kv machine and 2400 r (mid-plane dose) by the 2 Mev. apparatus. In March, 1956, four years following radiation therapy, the patient developed fatigue and pallor. However, he did not seek medical advice until November, 1956, when he was admitted to the hospital and found to have a severe anemia, leukopenia and thrombocytopenia. Peripheral blood smears showed no evidence of leukemia, but bone marrow aspiration revealed a myeloblastic proliferation. In March, 1957, following a very stormy course, the patient died, and an autopsy confirmed the diagnosis of acute myeloblastic leukemia. At post-mortem examination there was no trace of the original cancer present.

Comment. This patient received a large dose of x-ray therapy directed to the paravertebral lymph nodes; consequently, a considerable amount of penetrating radiation was delivered to the vertebral bone marrow. After a latent period of four years, acute myelogenous leukemia, characterized by a pancytopenic onset, developed. This case is very similar to many of the leukemia cases reported in the x-ray-treated spondylitis patients and may be considered as a "classic" example of radiation-induced leukemia.

Case 2.—F.H., a 59 year old male, had a testicular embryonic carcinoma removed in 1944. Radical removal of paravertebral lymph nodes revealed no metastatic disease. Following operation, during a period of four months, x-ray therapy consisting of 12,300 r (in air) was directed to the paravertebral lymph nodes. The patient was well until 1957, when he developed a severe anemia accompanied by thrombocytopenia and leukopenia.
Bone marrow biopsy in July, 1957, showed a relatively scanty marrow, but the cellular population consisted of very immature myeloid cells, and a diagnosis of acute myelogenous leukemia was established.

Subsequently the patient was treated with transfusions for the anemia. However, in April, 1958 a marked leukocytosis with numerous immature myeloid cells developed. Owing to a severe thrombocytopenia, corticoid as well as 6-mercaptopurine therapy was instituted. The patient is alive and moderately well controlled at the present time.

COMMENT. This patient received a large amount of x-ray to the vertebral marrow; except for the more prolonged latent period, the development of disease in this patient was very similar to that in case 1.

Case 3.—G.S., a 66 year old female housewife, had a very complicated medical history, with numerous hospital admissions for diagnostic studies and surgery. In 1938, following removal of a benign breast tumor, the patient received x-ray therapy over the chest area; the details of this treatment were not available. From 1938 to 1952 she had many diagnostic x-ray studies, including x-rays of the spine, pelvis, chest and extremities; also several intravenous pyelograms, gall bladder studies and at least seven complete G.I. series with fluoroscopic examinations. In 1955 and 1956 x-ray therapy, consisting of 1800 r (in air) was administered for bursitis and arthritis involving the cervical vertebrae. In August, 1956 the patient became acutely ill, and blood studies showed a picture of myeloblastic leukemia. Following an acute course of two-and-a-half months the patient expired, and autopsy confirmed the clinical diagnosis.

COMMENT. In this case an accurate estimation of the radiation dosage was impossible, and the contribution of the diagnostic x-ray was particularly difficult to evaluate. Nevertheless, she probably received a minimum of 2,000 r (in air), and most of the therapeutic radiation was delivered to the chest and cervical areas. Since radiation exposure in this case extended over a period of 18 years and x-ray therapy was given up to a few months before the onset of leukemia, the latent period was impossible to estimate.

Case 4.—H.S., a 66 year old female, was treated in 1935 for bleeding uterine fibroids with a total dose of 1600 r (in air) to the pelvis and lower abdomen. There was no other x-ray exposure except for gall bladder studies in 1955. In November, 1956, the patient began to feel poorly, and in January, 1957 she was admitted to the hospital. A blood picture of acute myelogenous leukemia was discovered, and the patient died two weeks after admission. Autopsy confirmed the diagnosis.

COMMENT. In this case the relatively small dose of x-ray, directed to the pelvis, and the 21 year latent period raises a question as to the validity of the etiologic role of ionizing radiation.

Case 5.—M.G., a 56 year old female, had a radical mastectomy for cancer of the breast in August, 1955. From October, 1955 to December 1955 she received x-ray treatments amounting to 2250 r (in air) directed to the left chest region. In February, 1957, she began to feel poorly and became obviously anemic. Blood studies showed a pancytopenia, but bone marrow aspiration revealed a marrow filled with immature cells consistent with the diagnosis of acute myelogenous leukemia. The patient died less than three months after the diagnosis was established. Permission for autopsy was denied.

COMMENT. In this case the radiation was delivered to the left chest area, and the latent period was relatively short, 16 to 18 months.

Case 6.—H.M., age 38, was of unusual interest. This patient was treated in a sanatorium for pulmonary tuberculosis from 1938 to 1944. During the later part of this illness, over
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a period of five years, she received weekly refills of a bilateral pneumothorax under direct chest fluoroscopy. In addition she had, of course, a large number of diagnostic chest x-rays.

In July, 1957, 17 years following the last fluoroscopic examination, the patient developed enlarged lymph glands and was found to have anemia, thrombocytopenia and leukopenia. Biopsy of an enlarged gland and of the bone marrow established a diagnosis of acute lymphatic leukemia. Following a course of eight months, during which she was treated with corticoids and 6-mercaptopurine, the patient died from intercurrent infections. Autopsy was not obtained.

COMMENT. This patient received x-ray for diagnostic rather than therapeutic reasons; however, the dose of ionizing radiation was in the therapeutic range. While difficult to estimate accurately, if it is assumed that she received from 5 to 10 r during each of approximately 250 fluoroscopic examinations, the patient may have received as much as 2000 r.

DISCUSSION

While the leukemogenic role of ionizing radiation has been demonstrated experimentally in animals, the proof in man has been largely circumstantial except for recent statistical evidence. The numbers of reported cases of radiation-induced leukemia are small and in many instances poorly substantiated. In a recent review of the world literature only 87 cases of leukemia due to exposure to x-ray, radium, thorium and $^{131}$ have been reported in the past 46 years. While the present concern with the adverse effects of ionizing radiation has probably served to overemphasize the role of radioactivity in leukemogenesis, nevertheless, that leukemia may be induced in man by ionizing radiation can hardly be disputed. However, from the available information, (except in a few unusual circumstances), it seems apparent that a considerable amount of irradiation is usually required to produce leukemia in adult humans.

The patients in this report were all treated with x-ray for malignant or benign disorders except for one case in which there was considerable exposure from unusually prolonged and frequent fluoroscopic examinations of the chest. In these patients the adequacy of the data on the amount and characteristics of x-ray exposure varied greatly. Best documented were two cases of testicular malignancy; these patients had large doses of deep x-ray therapy delivered to the paravertebral regions. In the other four cases the details of x-ray therapy were meager, and the radiation was directed to the chest in three instances and to the pelvis and lower abdomen in one case. (See table 1.)

An outstanding feature of radiation leukemogenesis is the latency of the disease. Usually a latent period (the time from irradiation to the development of clinical or hematologic evidence of leukemia) of at least a year elapses before leukemia develops. In the most adequately studied groups, the Japanese survivors of the atomic bomb and the British cases treated for spondylitis, latent periods for most cases fell between three and 10 years. However, a variety of factors such as age, dose, area irradiated, etc., may influence latency. Comparatively little is known concerning this problem in humans. In these six patients, latent periods were variable, extending from 18 months to 21 years. In one case (case 3), owing to the intermittent nature of radiation exposure, it was not possible to estimate the latent period.
### Table 1.—Summary of Data on Patients with Leukemia Following Exposure to X-Ray

<table>
<thead>
<tr>
<th>Patient, Age, Sex</th>
<th>Original Diagnosis</th>
<th>Radiation Data</th>
<th>Clinical Features</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.M., 38 F</td>
<td>Pulmonary tuberculosis</td>
<td>1939-1944, Both chest areas 2000 r (?) (fluoroscopic)</td>
<td>July 1957, March 5, 1958</td>
<td>Acute lymphocytic 17 yr.</td>
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</table>
In all six patients the disease was acute; four patients had myeloid, one monocytic and one lymphocytic leukemia. It is noteworthy that four of the six cases began with a pancytopenic onset and that the diagnosis in three of these patients was established only following bone marrow aspiration or biopsy. The hypoplastic onset has been a feature of many reported cases of radiation-induced leukemia, especially in the leukemias occurring in the irradiated spondylitics in England. This phenomenon is of great radio-biologic interest; moreover, since this type of hematologic picture may lead to an erroneous diagnosis of aplastic anemia, it is of practical importance also.

In man an understanding of radiation-induced leukemia will be achieved only by acquisition of much more well documented information, not only of the clinical and hematologic findings, but especially in regard to the dosage and characteristics of the radiation exposure. In the present state of our knowledge, whether or not the evidence can be accepted as valid, it is important that all cases of leukemia attributed to ionizing radiation should be meticulously reported.

**Summary**

1. Six cases of leukemia occurring in patients exposed to varying doses of x-ray are reported in this article.
2. The difficulties in evaluating the dosage of radiation is well illustrated in most of these cases.
3. Latent periods were variable and difficult to estimate accurately. It is pointed out that the latent periods in radiation-induced leukemia usually are from three to 10 years in length.
4. All cases in this group were acute leukemias; in four the onset simulated aplastic anemia and diagnosis was verified only after bone marrow aspiration or biopsy.
5. The difficulties in establishing criteria for the diagnosis of radiation-induced leukemia in the present inadequate state of our knowledge are pointed out. In all cases of leukemia attributed to ionizing irradiation it is urgently necessary to publish all information in as complete detail as possible.

**Summario in Interlingua**

1. Es reportate sex casos de leucemia occurrente in subjectos exponite a variis doses de radios X.
2. Le difficultate de evalutar le dosage de radiation correctemente es ben illustrate per le majoritate del casos reportate.
3. Le periodos de latentia eseva pauc uniforme a difficile a estimar accuratemente. Es signalate que le periodos de latentia in leucemia inducite per radiation es usualmente inter tres e 10 anos.
4. In omne le casos de iste gruppo il se tractava de leucemia acute. In quatro le morbo s’mulava, al tempore de su declaracion, le syndrome de anemia aplastic, e le diagnose eseva establite correctemente solo super le base de aspiration medullar o de biopsia.
5. Es signalate le difficultates de estableciri criterios pro le diagnose de leucemia inducite per radiation, viste le currente inadequate stato de nostro
cognoscentias. In omne casos de leucemia attribuite a irradiation ionisante, il es urgentemente necessari publicar omne le informationes in le plus complete detalio possibile.

REFERENCES


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