Acute Leukemia Following Localized Irradiation for Carcinoma of the Larynx

By Richard K. Karchmer, Glyn G. Caldwell, and Tom D. Y. Chin

During a 5-yr leukemia surveillance study in the metropolitan Kansas City area, four patients who had previously received irradiation therapy for carcinoma of the larynx developed acute leukemia. The frequency of occurrence represents a significant increase of the observed over the expected. These findings indicate that, even with such localized radiotherapy, the possibility of irradiation-induced leukemia must be considered in therapeutic decisions.

Acute and chronic leukemia following irradiation has been well documented by the Atomic Bomb Casualty Commission reports.1,2 A recent study by Chan and McBride3 reviewed the occurrence of leukemia in Hodgkin's disease and implied that acute leukemia may be a complication of irradiation therapy affecting survivors of this disease. Poth et al.4 recently described the development of acute leukemia following localized radiotherapy for malignancy in four patients. Although this last report suggested an increased frequency of acute leukemia in patients given high-dose irradiation for localized neoplasms, no statistical conclusions could be made because the population at risk was unknown.

Because of the above implications, we have reviewed the data collected during the first 5 yr of leukemia surveillance in the metropolitan Kansas City area.5 Patients' names, with the diagnosis of leukemia, were obtained from hospital record rooms and tumor registries, records of practicing physicians, and death certificates. A physician then reviewed each hospital chart to obtain and verify the data. These data included 543 patients diagnosed with leukemia during the period January 1966 through December 1970. The patient or a relative was asked to complete a questionnaire which included information about the history of a previous malignancy or if the patient had received irradiation therapy. Four patients were found with a history of carcinoma of the larynx, and all four had received irradiation therapy for these neoplasms. The hospital records on these four patients were reviewed again by one of the authors (R.K.K.). Information was available on the total numbers of acute leukemias and laryngeal carcinomas in the metropolitan Kansas City area during the 5-yr period. Therefore, it was possible to determine the probability of these patients repre-
senting an excess over the expected number of irradiation patients with laryngeal carcinoma to develop leukemia.

PATIENTS (See Table 1)

Patient No. 1

This 74-yr-old white male entered the hospital in February 1967 with a 2-mo history of hoarseness. Laryngoscopy showed a tumor of the right true vocal cord. Multiple biopsies revealed welldifferentiated squamous cell carcinoma. A complete blood count (CBC) was normal. He received 6000 rads tumor dose with 60 Co to the larynx over a 6-wk period. In August 1967, a second laryngoscopy and biopsy revealed involvement of both cords. The patient refused surgery, and no more irradiation could have been safely given. A second CBC was normal. In December 1967, the patient underwent an intralaryngeal excision of the tumor, which was now extending into the anterior commissure and blocking his airway. In May 1968, he rapidly became weaker, and his CBC on admission showed the following: hemoglobin, 7.7 g/100 ml; hematocrit, 21%; and white blood count (WBC), 120,000/cu mm, with 40% of the cells being blasts of myelocytic or monocytic origin. The blast cells showed an increased nuclear-cytoplasmic ratio, multiple nucleoli, and Auer rods. The family refused a bone marrow aspiration. The patient developed a respiratory infection and died. No autopsy was performed.

Patient No. 2

This 64-yr-old white male entered the hospital in April 1963 complaining of hoarseness. Laryngoscopy and biopsy revealed squamous cell carcinoma of the anterior portion of the true cord and the laryngeal surface of the epiglottis. He underwent a wide-field laryngectomy, and a right jugular lymph node was found to contain tumor cells. He then received 3000 rads with 60 Co to the right neck area. At this time, the CBC was normal. One year later he developed a metastasis to a node in the left neck and underwent radical neck dissection. He was in good health until April 1967, when he developed weakness and loss of appetite. There was no evidence of recurrence of his cancer, but his CBC showed a hemoglobin of 8.6 g/100 ml, a hematocrit of 27%, and a WBC of 25,300/cu mm, with 5% bands, 33% mature granulocytes, 27% lymphocytes, and 35% mononuclear cells. Many of the latter cells were blasts. The bone marrow study showed a markedly increased number of myeloblasts with the presence of Auer rods. Six months later the patient died of respiratory failure, and an autopsy was not performed. At death there was no obvious evidence of a recurrence of his laryngeal neoplasm.

Patient No. 3

This 83-yr-old white male entered the hospital in April 1969 with a 6-mo history of hoarseness. Laryngoscopy and biopsy revealed that the left cord was infiltrated by squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date 60 Co Therapy Begun (yr)</th>
<th>Neck Area Treated</th>
<th>Port Size (cm)</th>
<th>Tumor Dose (rads)</th>
<th>Marrow Dose (rads)</th>
<th>Amount of Marrow Irradiated</th>
<th>Date Leukemia Diagnosed (yr)</th>
<th>Latent Period (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1967</td>
<td>Bilateral</td>
<td>6 (diam)</td>
<td>6068</td>
<td>Midcervical spine</td>
<td>5</td>
<td>1968</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>1963</td>
<td>Right lateral</td>
<td>3000</td>
<td>C2-7</td>
<td>4</td>
<td>1967</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1969</td>
<td>Bilateral</td>
<td>5 x 5</td>
<td>6000</td>
<td>C4,5,6</td>
<td>12</td>
<td>1970</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1967</td>
<td>Bilateral</td>
<td>4 x 4</td>
<td>6000</td>
<td>C4,5,6</td>
<td>6</td>
<td>1968</td>
<td>9</td>
</tr>
</tbody>
</table>

*Estimate by radiotherapist treating patient.
†Time between irradiation and onset of leukemia.
ACUTE LEUKEMIA

He then received 6000 rads to the larynx with 60 Co in 30 treatments over a 7-wk period. Prior to this therapy, his CBC was normal. In November 1970, he was pancytopenic, with a hemoglobin of 7.7 g/100 ml, a hematocrit of 24.7%, decreased platelets, and a WBC of 2,400 cu mm, with 47%, mature granulocytes, 3%, bands, 2%, basophils, 41% lymphocytes, 2% monocytes, and 5% blast forms. Indirect laryngoscopy revealed no evidence of recurrent neoplasm, and there were no palpable nodes. In December 1970, he was admitted with hemoptysis and lower intestinal bleeding. His peripheral smear now showed 52% blast forms, with a WBC of 13,400/cu mm. He developed pneumonia and sepsis and later died. His autopsy did reveal some tumor remaining in the vocal cord, but showed no evidence of regional metastasis. Poorly differentiated leukemic infiltrates were present in the bone marrow, liver, and spleen.

Patient No. 4

This 79-yr-old white male entered the hospital in October 1967 with hoarseness and a sore throat. No nodes were palpable, and his CBC showed a hemoglobin of 16 g/100 ml, a hematocrit of 47%, and a WBC of 31,800/cu mm, with 10%, mature granulocytes, 1% bands, and 89%, mature lymphocytes. Laryngoscopy revealed a polypoid lesion of the left vocal cord. The biopsy showed squamous cell carcinoma, and the patient received 6000 rads with 60 Co to the larynx in 30 treatments over a 6-wk period. In June 1968, a tracheotomy was performed because of difficulty with breathing. A residual tumor was found growing across the glottis. His CBC was essentially unchanged, but generalized lymphadenopathy was now present. A bone marrow aspiration revealed 90% lymphocytes, many of which were large and immature and exhibited multiple nucleoli. Both the pathologist and the hematologist felt that these immature lymphocytes were different from the cells in the patient’s peripheral smear of October 1967. He was classified as an acute lymphocytic leukemic. Two months later he died of a respiratory infection. An autopsy substantiated the above diagnosis.

DISCUSSION

Each of the four patients described in this study received a large amount of irradiation to a small area of the head and neck and later developed acute leukemia. Each had well-documented carcinoma of the larynx. Three of the four patients had a normal CBC before receiving radiotherapy. The diagnosis of leukemia in patient 1 was determined from the blasts in the peripheral smear and the presence of Auer rods in these blasts. Patient 2 was diagnosed from the bone marrow aspiration. At autopsy, patient 3 had acute leukemic infiltrates in several organs. Patient 4 almost certainly had chronic lymphocytic leukemia prior to this therapy; however, following treatment, his blood picture changed, and the bone marrow then showed many immature cells different from the previous predominant cell type. McPhedran and Heath reviewed the question of whether a blast phase occurs during the course of chronic lymphocytic leukemia, and they concluded a true blast phase probably does not exist or is quite rare. The change in the blood picture in patient 4 could have been secondary to the irradiation therapy he received.

Patients with carcinoma of the larynx have no known natural predisposition to developing leukemia. The many studies done on carcinoma of the larynx have not specifically mentioned leukemia as a significant complication. However, Poth et al. have described four patients who received high-dose irradiation therapy for various malignancies prior to developing acute leukemia, and one of these patients had received his therapy for carcinoma of the larynx. Also, in a study by Lathrop of supervoltage irradiation for carcinoma of the larynx, seven of 12 stage-I patients who died of other diseases died of another primary cancer. The tissue types were not mentioned. Our four patients had no obvious
immunologic or hereditary defect which would have increased the risk of developing leukemia,\textsuperscript{10} and none of them received any cancer chemotherapy prior to the onset of the leukemia.

Thus, the development of leukemia in these four cases of laryngeal carcinoma seemed unusual. The four patients received a minimum of 3000 rads of localized radiotherapy (see Table 1), the one obvious leukemogenic factor. The average latent period of 23 mo was shorter than previously described for apparent irradiation-induced leukemia;\textsuperscript{1,2} however, age, sex, dose, and area of exposure can influence radiation leukemogenesis.\textsuperscript{11} The mean age at diagnosis in these four patients was 75 yr, which is later than the mean age usually observed in laryngeal carcinoma. Furthermore, only small areas of cervical marrow received irradiation (see Table 1), but vertebral marrow is the most cellular and responsive in the elderly.\textsuperscript{12}

Since three of these four patients received irradiation and then developed leukemia over the 5 yr (1966–1970) of the leukemia study, the statistical significance of these three cases could be determined. Data were collected from all cases of laryngeal carcinoma first diagnosed during 1966–1970. The record rooms, tumor registries, and pathology departments of the same 35 hospitals participating in the leukemia surveillance study were asked to report all patients with carcinoma of the larynx, giving their age, sex, pathologic diagnosis, date of diagnosis, and method of treatment (e.g., surgery, radiotherapy, or both). Data were collected from 285 patients with squamous cell carcinoma of the larynx during the 5-yr period: 88\textperthousand of these were males and 12\textperthousand were females, with the mean age being 61 yr. Applying the annual age-adjusted rate for carcinoma of the larynx in 1960 in New York\textsuperscript{13} to the 1970 metropolitan Kansas City population,\textsuperscript{14,15} 310 individuals would be expected to have developed carcinoma of the larynx over the 5-yr period. The 285 patients in this study are, therefore, consistent with a complete collection.

Of the 285 reported cases, 101 received irradiation to the larynx. In 60 cases, the type of therapy was not reported. Thus, 161 patients had cancer and could have received irradiation. None of the nonirradiation patients have developed acute leukemia. Applying the age-sex specific rates for acute leukemia in Kansas City\textsuperscript{16} to the age-sex distribution of the 161 reported cases, approximately 0.07 patients would be expected to have developed acute leukemia from the date of irradiation therapy to the end of the study in December 1970. The occurrence of three cases thus represents a significant increase of the observed over the expected: the probability of as many as three cases occurring by chance is $p < 0.001$ (Poisson distribution).

This study suggests a definite increased incidence of acute leukemia following irradiation for even small, localized neoplasms in which the bone marrow may be affected.

Previous studies are difficult to compare because of differences in irradiation dose, the temporal and spatial distribution of the dose, and patient selection. However, epidemiologic surveys of increased leukemia from diagnostic x-rays\textsuperscript{17,18} and radiotherapy\textsuperscript{19,20} and the cases presented here support the hypothesis that the risk of leukemia induction is proportional to the total energy absorbed by the marrow, irrespective of the volume of marrow involved.\textsuperscript{19}
Patients, especially the elderly, receiving irradiation therapy for carcinoma of the larynx may have an increased risk of developing leukemia; therefore, patients who have received irradiation must be adequately followed, and any change in their clinical status must not automatically be assumed to be a recurrence of their original neoplasm. This study also emphasizes the importance of epidemiologic surveillance for recognizing causes and effects in any treatment program.

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REFERENCES

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