Attempted Transmission of Acute Leukemia from Man to Man by the Sternal Marrow Route

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Previous attempts to transmit human leukemia from man to man with blood, cellular emulsions, from spleen and lymph nodules had completely failed. In these experiments the author (3) used the subcutaneous or intravenous route, with a subsequent period of observation of 24 months after the inoculations. With the subcutaneous or intravenous route of transmission the leukemic "agent" might not have come into contact with sufficient suitable and susceptible cells of the bone marrow. To place the material in contact with bone marrow cells the intrasternal marrow route of inoculation was chosen.

In the experiments described in this paper I used sternal bone marrow from untreated cases of acute leukemia for the transmissions. It was hoped to gain information about this special form of leukemia which differs from the chronic form by its rapid fulminant course, the age group involved, the specialized production of one cell-type only and the lack of response to any known treatment. The recipients of the leukemic material were human volunteers suffering from carcinoma of the oral cavity (tongue, pharynx, etc.). This did not exclude a priori the possibility of "takes," as the co-existence of leukemia and carcinoma in the same patient is known. Twenty such cases are recorded in the literature by Morrison, Feldman and Samwick (2), and by Berk and Movitt (1) who described a case of laryngeal carcinoma complicated by lymphoid leukemia. Two additional cases, one in a woman of 67 suffering from chronic lymphatic leukemia and sero-anaplastic carcinoma of the ovary, and one in a man of 56 suffering with chronic myeloid leukemia and a rectal adenocarcinoma, were observed in Adelaide.

SUBJECTS AND METHODS

Human volunteers who had been treated for squamous cell carcinoma of the tongue or pharynx were the recipients of the leukemic material. The diagnosis of carcinoma of the tongue was established by clinical examination and biopsy. The tumors were all treated with surgery and radium needling. Before the transmission attempts, the blood and sternal marrow of these cancer cases were examined. At the time of transmission 3 such cancer cases were placed on tables. The area over the manubrium sterni was anesthetized with 4 cc. of a 2 per cent novocain solution. A sternal puncture needle was inserted in each manubrium. Approximately 0.2 cc. of the marrow was aspirated for marrow films. The stiletto was then re-inserted in the sternal puncture needle in the sternum.

Each case of acute human leukemia was prepared in the same way—a sternal puncture needle was inserted. Five cubic centimeters of the cellular sternal marrow were aspirated with a 10 cc. Record syringe. This material was injected through the already inserted needles into the sternal marrow of the recipients within a few seconds, and without any anti-coagulant, each recipient receiving approximately 1.5 cc. of leukemic bone marrow. The last drops of the aspirated leukemic material were used for marrow films and bacteriological examinations. Blood plates inoculated with sternal marrow from all 4 donors were found to be sterile after incubation for 48 hours. This procedure was repeated 4 times. The progress of the recipients was closely watched clinically and hematologically. At first daily, then weekly, later monthly blood counts, and also sternal marrow films at longer intervals, augmented the clinical examinations. In case of death of the patients with acute leukemias or of the recipients, complete or partial necropsies were performed.

The first donor was a boy of 10. He came to the hospital with a history of a sore throat, headache and breathlessness. The patient had bleeding, spongy gums, fever, a severe anemia, a high leukocyte count and an enlarged painful liver. The spleen was not palpable. The patient died after 29 days in the hospital. A postmortem examination was refused by the relatives. The bone marrow of this patient was used for transmission on the third day of his hospitalization. The peripheral blood on that day showed only 6.24 gm./per cent hemoglobin, and a leukocyte count of 103,000 of which 91 per cent were myeloblasts.
The sternal marrow reflected, with 90 per cent, the same predominance of myeloblasts.

Recipients.—(1) A man of 67, treated with radium needles 17 years ago for a squamous cell carcinoma of the lip, and 6 months ago for a squamous cell carcinoma of the tongue. The patient had received a course of deep x-rays to the neck 3 months prior to the sternal inoculation.

(2) Man aged 70 (Wassermann reaction positive). The patient was treated with radium needles 5 years ago for a squamous cell carcinoma of the tongue, had deep x-ray therapy to the neck 4 years ago and, finally, had a resection of the tongue 3 years ago (apart from anti-luetic treatment 5 years ago).

(3) Man aged 72 (Wassermann reaction positive). The patient was treated with radium needles for squamous cell carcinoma of the tongue 40 months ago followed by excision of the lymph nodes of the neck 3 years prior to the sternal inoculation. This patient developed a mild secondary anemia with an increased monocyte count in the peripheral blood within 15 months of the inoculation. On examination an adenocarcinoma of the rectum was found, confirmed by biopsy and treated with colostomy. The patient died 181 days after the sternal inoculation from his carcinoma without any indication of leukemic lesions in bone marrow or blood.

The first two cases are still alive and clinically quite well without signs of leukemic lesions in blood or bone marrow 35 months after the sternal inoculations.

The second donor, a young man of 16, came to the hospital with a history of gastritis. He suffered from spongy gums, increasing anemia, and high fever. The examination of blood and bone marrow showed a marked predominance of myeloblasts with 60 per cent myeloblasts. The bone marrow of this case was used for inoculations on the 19th day of hospitalization. The peripheral blood showed 5.3 gm./per cent hemoglobin, 11,200 of which 99 per cent were myeloblasts. The patient died 26 months after the inoculation gave no evidence of leukemic lesions in the internal organs.

Recipients.—(1) A man of 45, treated 12 months ago for a squamous cell carcinoma of the tongue with biopsy and radium needling. The lymph nodes of the neck were excised 10 months ago for a secondary deposit, followed by a course of deep x-ray 2 months later. For the last 8 months the patient was without further noticeable recurrences.

(2) A man of 88, treated with radium needling and deep x-rays for a squamous cell carcinoma of the tongue 3 years ago. The patient had secondary deposits in the lymph nodes of the neck, removed 13 months ago.

(3) A man of 67, treated with radium needles for squamous cell carcinoma of the tongue 15 months ago, followed by a course of deep x-rays to the neck 9 months later and excision of the lymph nodes of the neck a week prior to the inoculation.

Blood and bone marrow of these 3 recipients before and up to 26 months after the inoculation gave no evidence of leukemic lesions, progressive anemia, splenic or lymph node enlargement, or lesions of the gums.

The third donor, a man of 41, came to the hospital with dental symptoms which had persisted for 3 weeks. On examination he had ulcerated spongy bleeding gums, a swinging temperature, an enlarged liver, a string of palpable lymph nodes in the neck, a progressive severe anemia and an increased leucocyte count. The patient died after 36 days in the hospital and at necropsy had the typical lesions of an acute myeloblastic leukemia, involving gums, lymph nodes, liver, spleen and bone marrow. The sternal marrow of this case was used for inoculations on the 19th day of hospitalization. The peripheral blood showed 5.3 gm./per cent hemoglobin, 24,000 leukocytes with 60 per cent myeloblasts. The bone marrow also showed a marked predominance of myeloblasts.

Recipients.—(1) A man of 52, treated for carcinoma of larynx 8 months ago with deep x-rays, treated for carcinoma of the tongue with radium needling just prior to treatment and 20 days after the sternal inoculation. Later, recurrences and secondary deposits of his carcinoma of larynx and tongue appeared. The patient died 108 days after the sternal inoculation from hemorrhages from his ulcerated throat studded with necrotic cancerous material. At necropsy no evidence of leukemic lesions was found in the internal organs.

(2) A man of 52, treated with radium needles 14 months ago for squamous cell carcinoma of epiglottis at the base of the tongue, followed by a course of deep x-rays to the neck 8 months prior to, and 10 days after, the intrasternal inoculation with leukemic material. This patient died 217 days after the inoculation from an aspirative pneumonia due to an ulcerated carcinomatous nodule in his throat. At necropsy no evidence of leukemic lesions was found in the internal organs.

(3) A man of 77, treated with radon needles 13 days after the sternal inoculation for a squamous cell carcinoma of the tongue extending to the floor of the
<table>
<thead>
<tr>
<th>Name</th>
<th>Preclinical history</th>
<th>Total duration of illness in days</th>
<th>Day of donation</th>
<th>Group</th>
<th>Hemoglobin</th>
<th>White blood cells</th>
<th>Blood count (day of donation)</th>
<th>Differential Cells</th>
<th>Bone marrow (day of donation)</th>
<th>Differential Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Male, aged 10 years) A. R.</td>
<td>Sore throat, Breathless, Headache 14 days</td>
<td>43</td>
<td>3rd</td>
<td>O (IV)</td>
<td>6.24</td>
<td>103,000</td>
<td>Polymorphs 2, Myelocytes 4, Myeloblasts 91, Normoblasts 3, Anisocytosis and macrocytosis of red blood cells</td>
<td>Polymorphs 2, Lymphocytes 2, Myelocytes 4, Myeloblasts 78, Lymphocytes 5, Normoblasts 10</td>
<td>Polymorphs 3, Metamyelocytes 1, Myelocytes 2, Myeloblasts 90, Lymphoblasts 2, Normoblasts 2, Erythroblasts 1</td>
<td></td>
</tr>
<tr>
<td>(Male, aged 16 years) K. F.</td>
<td>Stomatitis 3 weeks</td>
<td>29</td>
<td>5th</td>
<td>B (III)</td>
<td>4.68</td>
<td>11,200</td>
<td>Polymorphs and Eosinophils 1, Myeloblasts 99, Normoblasts present, Platelets scanty</td>
<td>Polymorphs 2, Lymphocytes 2, Myelocytes 4, Myeloblasts 78, Lymphocytes 5, Normoblasts 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Male, aged 41 years) W. G.</td>
<td>Dental symptoms 3 weeks</td>
<td>57</td>
<td>19th</td>
<td>A (II)</td>
<td>5.3</td>
<td>24,000</td>
<td>Polymorphs 12, Lymphocytes 20, Monocytes 4, Normoblasts 2, Myelocytes 2, Myeloblasts 60</td>
<td>Polymorphs 3, Metamyelocytes 1, Myelocytes 2, Myeloblasts 90, Lymphoblasts 2, Normoblasts 2, Erythroblasts 1</td>
<td></td>
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</tr>
<tr>
<td>(Male, aged 21 years) P. B.</td>
<td>Ulcerated gums, Sore throat</td>
<td>90</td>
<td>36th</td>
<td>O (IV)</td>
<td>11.7</td>
<td>347,000</td>
<td>&quot;Blasts&quot; 97, Myelocytes 3, Myeloblasts 3, Normoblasts</td>
<td>Polymorphs 3, Metamyelocytes 1, Myelocytes 2, Myeloblasts 90, Lymphoblasts 2, Normoblasts 2, Erythroblasts 1</td>
<td></td>
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mouth, and 5 months after with a course of deep x-rays to the neck. This patient is still alive after 24 months and without symptoms or lesions in blood or bone marrow which could be related to leukemia.

The fourth donor was a man of 21 with a history of a sore throat and agranulocytosis for 10 days. The patient arrived in the hospital with ulcerated gums, a painful liver and spleen, a moderate anemia and enlargement of the lymph nodes in the supravclavicular fossa. Sternal marrow was used for transmission on the 36th day of illness. The blood showed hemoglobin of 11.7 gm./per cent, a leucocyte count of 347,000 with 97 per cent of naked nuclei of the “blast” series. The bone marrow on that occasion was very cellular and 90 per cent of all nucleated elements consisted of these primitive “blasts.” The patient died 90 days after admission to hospital with anemia, enlarged spleen, liver, large mediastinal tumor and generalized enlargement of lymph nodes. The microscopical examination of liver, bone marrow, lymph nodes and mediastinal tumor left no doubt that this case was an acute lymphoid and not a myeloblastic leukemia.

Recipients.—(1) A man of 48, treated with radon needles for squamous cell carcinoma of the tongue 5 months prior to, and with excision of the lymph nodes of the neck 20 days after, the sternal inoculation. The patient is apparently quite well 21 months after the sternal inoculation. There is no evidence of leukemic lesions in blood, or bone marrow.

(2) A man of 70, treated with radon needles for a squamous cell carcinoma of the tongue 74 months prior to, and with excision of the glands 20 days prior to, the sternal inoculation. This patient is also apparently quite well 21 months after the sternal inoculation without any indication of leukemic lesions.

(3) A man of 67, treated with radium needles for a squamous cell carcinoma of the tongue 11 months prior to, and with excision of the lymph nodes of the neck 11 days prior to, the sternal inoculation. This patient died 101 days after the implantation with a recurrent carcinoma and aspirative pneumonia. At autopsy no evidence of leukemic lesions was discovered in the internal organs.

Details relating to the leukemia donors are summarized in Table I.

RESULTS

No evidence could be detected clinically or hematologically that the implantations of leukemic bone marrow had any effect whatever on the recipients. No abnormal course or complication of the recipients' carcinoma, no change in the recipients' temperature, lymph nodes, spleen, leukocytes, hemoglobin or bone marrow could be detected during the time of observation which could possibly be attributed to leukemia. In no instance could immature leukocytes be detected in the peripheral blood. The percentage of myelocytes and especially myeloblasts did not increase in the bone marrow in any of the recipients. The hemoglobin and total leucocyte counts varied slightly. In every instance secondary deposits of the pre-existing carcinoma undergoing necrosis with sloughing or other complications such as aspirative pneumonia or hemorrhage were responsible. The findings of the repeated blood and bone marrow examinations were tabulated, but as only insignificant changes were observed this large collection of data is being omitted from publication.

It is obvious that the transmission attempts failed. However much the acute and chronic forms of leukemia differ clinically, both are apparently not transmissible under the circumstances described. Human leukemia resembles very closely the leukemia in mice and birds. In mice inbred strains are required for successful transmissions, but this is not so for birds. The lack of transmissibility of acute human leukemia has its counterpart in animal leukosis. It is an indication that the acute cases are only special forms of the chronic ones. They are different clinical manifestations of the same process appearing at an earlier date with a more rapid course.

The lack of “takes” in the described transmission attempts might be due to several factors such as the different genetic structure of the recipients from the donors, the age group of the recipients, their state of nutrition, and immunity to the implants due to the presence of a cancer. It is to be recalled also that as some virus-like agents, such as the milk factor, have an incubation period of about one-half the lifetime of the animal, it might be necessary to observe for a longer time than the periods recorded here, human subjects into whom leukemic material had been injected.

SUMMARY

Acute untreated human leukemia could not be transmitted with cellular sternal marrow by the sternal marrow route from man to man. No further evidence to separate acute and chronic leukemia, in spite of their clinical difference, could be brought forward. No evidence of a transmissible virus as cause of acute leukemia in man was detected.

REFERENCES


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