Chronic Granulocytic Leukemia and Cancer

Report of a Case

By Helen B. Angus and Frederick W. Gunz

In this paper we describe the case of a man who, at the age of 34, was first diagnosed as suffering from chronic granulocytic leukemia and who died aged 41 from carcinoma of the pancreas with the leukemia in remission. During the 7 1/4-year course of his illness he was extensively treated with radio- and chemotherapy. In view of their mutagenic properties the question is now raised whether the carcinoma could have been induced by these agents, or whether it was of coincidental origin.

Case Report

An engineer aged 34 was admitted to hospital on August 19th, 1954 because, for the past 36 hours, he had suffered an acute attack of continuous priapism. For about 2 months he had noticed increasing lassitude and repeated but shortlived attacks of priapism. He was pale and distressed, and his spleen was felt 2.5 cm. below the left costal margin. A few small lymph nodes were palpable in the axillae and groins. His hemoglobin level was 12.0 Gm. per 100 ml, hematocrit 33 per cent, leukocytes 275,000 per cu mm., with 61 per cent neutrophils, 33 per cent myelocytes, 2 per cent myeloblasts, 1 per cent eosinophils, 2 per cent basophils and 1 per cent lymphocytes. The sternal marrow was typical of chronic granulocytic leukemia.

He was treated by means of x-irradiation of the spleen and of the perineum, and the painful erection gradually subsided. It never returned, but he became impotent. He was discharged from hospital on September 9th, and soon afterwards returned to work. During the further course of his illness he remained well until the terminal stages.

The hematologic findings and treatment are shown in figure 1. He received two courses of deep x-ray therapy to the spleen totaling 4850 r, 400 r to the perineum, and 29.4 mc. of radiophosphorus. When radio-resistance became apparent, chemotherapy was given by means of intermittent courses of busulfan totaling 380 mg. Early in 1961 the patient entered the acute "blastic" phase of the illness heralded by lassitude, a fall in the hematocrit and platelet count and the appearance of large numbers of blasts in the marrow and blood. Treatment was changed to 6-mercaptopurine (6-MP). He became critically ill, there was a pancytopenia, and Staphylococcus aureus was grown from the blood. 6-MP was discontinued and prednisone and antibiotics given. A complete clinical and hematologic remission ensued and the patient returned to his normal work. Maintenance therapy with 6-MP and prednisone was instituted, and he received altogether 14.2 Gm. and 2.31 Gm. respectively of these drugs.

Four months later the patient began to complain of intermittent attacks of abdominal pain, at first thought to be due to peptic ulceration. A barium meal was normal as were the blood and myelogram. Gradually, hepatic enlargement developed, followed by abdominal distension and jaundice. The spleen was not palpable. Biopsy disclosed invasion of the liver by carcinoma cells. The patient's condition now deteriorated rapidly and he died on November 28th, 1961. An autopsy revealed a grossly enlarged liver weighing 3300 Gm. with many tumor deposits throughout the parenchyma. These were found to be secondary to a 2.5 cm. tumor of the pancreas lying in the body of the organ near the head;

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histologically it was an adenocarcinoma of high malignancy. Small secondary growths were situated in the lymph nodes and lungs. The spleen was moderately enlarged, weighing 450 Gm., and contained several obvious tumor deposits. It also showed some leukemic infiltration. The bone marrow was moderately cellular; there were some groups of blasts separated by areas of low cellularity, as well as tumor deposits.

**DISCUSSION**

Points of interest in this case history are the relatively long survival, the occurrence of a complete remission in the acute phase, and the association of leukemia with a rare form of carcinoma.

A 7-year survival from diagnosis of chronic granulocytic leukemia may be expected to occur in upward of 10 per cent of adequately treated cases (Os- good et al.). Complete remissions are rare in the acute phase (Dameshek and Gunz). The present patient had shown great sensitivity to all forms of therapy throughout his course. His myeloid cells had an unusual chromosome constitution in that they showed two abnormal acrocentric chromosomes, the Ph1 and a minute form not previously described (Adams et al.). It is possible that this particular chromosome constitution may have been in some way favorable for a good response to therapy.

The association of chronic granulocytic leukemia and pancreatic carcinoma must be extremely rare. The mortality in New Zealand from all leukemias is 5 per 100,000 males aged 30–40; that from carcinoma of the pancreas is 2 per 100,000 males aged 40 to 45. The chance of both conditions occurring in the same patient would therefore be 1 in 10⁸ if there were complete independence between them. In view of the remoteness of this chance it must be asked if there is any reason why they should be linked and thus more frequently associated.

There is good evidence to show that patients with chronic lymphocytic leukemia have an unusually high incidence of past or concurrent personal cancer of all kinds (Beresford, Lawrence and Donald, Moertel and Hage-
dorn, Pisciotta and Hirschboeck, Gunz), but the same has not been found in chronic granulocytic leukemia. Specifically, a search of the more recent literature has discovered no case of leukemia in a total of 1355 cases of carcinoma of the pancreas. While it is possible that some patients with chronic lymphocytic leukemia may be genetically predisposed to developing cancer, this is probably not so in chronic granulocytic leukemia.

The patient was treated with large doses of radiation and with relatively smaller doses of busulfan. Both are mutagenic and produce visible chromosome abnormalities (Koller, Fahmy and Fahmy). Radiation was given both locally to the spleen and to the whole body. The interval between radiation and death was from 2 to 7 years. The local radiation was given over two fields, 15 x 10 cm., one anteriorly and one posteriorly, the radiation factors being 230KV, HVL 1.5 mm. Cu, 50 cm. FSD. It was calculated that the tail of the pancreas received approximately 2000 r, the head 500 r, and the body intermediate doses. This exposure may have been of significance, since in another case of chronic granulocytic leukemia treated by splenic irradiation (Waller) it was shown at autopsy that the pancreas was the seat of giant nuclei, nuclear polymorphism and polyploidy. A neoplastic transformation might well have followed as the next step in such a case, especially when later there was also exposure to beta radiation and a chemical mutagen, as in our case.

Busulfan given orally is readily excreted in the urine, but little is known about its distribution in the human body (Nakarni et al.). In the present case the total dose was not large, and moreover the drug was first administered only 19 months before death. For these reasons busulfan appears unlikely to have been solely responsible for the neoplastic change, but it could have accentuated changes already under way in a synergistic fashion. Although 6-MP was given in large dosage, the interval between its administration and the patient’s death was even shorter than in the case of busulfan.

Recent methods of treating chronic leukemia have entailed the administration of rather large quantities of radiation and of chemotherapeutic agents (Osgood et al., Haut et al., Gunz et al.) and promise to lead to not inconsiderable prolongation of life. Sizeable numbers of patients can now be expected to survive 5 years and more from the beginning of treatment. In these circumstances it appears wise to consider the possibility that the therapeutic agents may themselves be capable of giving rise to neoplasms in the treated patients. Although the lesion in our case cannot be attributed with certainty to such activity, its occurrence suggests the need for close observation of patients under long-term treatment, and especially for detailed data on all cases in which carcinomas and leukemia have coexisted in the same patient.

**Summary**

A man of 34 with chronic granulocytic leukemia survived for 7 1/4 years from diagnosis and died from carcinoma of the pancreas. It appears possible that this tumor was caused by the treatment given for the control of the leukemia.

*These doses were kindly calculated by Mr. J. J. Tait, M.Sc., Senior Physicist, Department of Radiotherapy, Christchurch Hospital.*
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