LYMPHATIC LEUKEMIA AND LYMPHATIC LEUKEMOID STATES IN CANCER OF THE STOMACH

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THE COEXISTENCE of leukemia and cancer of the stomach in the same individual has been reported a few times (Burg, myeloid leukemia; Zadek, myeloid leukemia; Saupe, aleukemic lymphatic leukemia; Penzold, lymphatic leukemia; Dustin, lymphatic leukemia; Kast, lymphatic leukemia; Svejda, aleukemic lymphatic leukemia). In Burg's and Zadek's cases the leukemic changes in the organs were very slight, which was ascribed to the intense treatment with radium, but otherwise the criteria for the diagnosis of leukemia seem to have been present in all these cases. A case of cancer of the stomach associated with lymphatic leukemia reported by Bichel may possibly have been a leukemic, lymphatic reaction (see later). At the Radium Center for Jutland we have observed 3 cases of cancer of the stomach in association with the blood picture of lymphatic leukemia.

CASE REPORTS

P. Chr. N. (Radium Center 1239/41) laborer, single, born 1877. After straining himself by lifting a heavy object in 1935, pains developed in the lumbar region. They recurred intermittently to 1941, when he again overstrained and the condition became acute. He was admitted to a medical service, where destructive processes and collapse of the eleventh and twelfth thoracic and fourth and fifth lumbar vertebrae were found. Swollen lymph nodes in the neck, axillae and groins were also found at this time. The leukocyte count was 250,000 per cu.mm., with 88 per cent lymphocytes. The latter were small, rich in chromatin, and with very scant cytoplasm. As the changes in the bones were thought to be leukemic, the patient was transferred to the Radium Center for radiation treatment. Roentgen irradiation to the spine relieved the pain somewhat, and at the same time the leukocytes dropped to about 12,000 per cu.mm., with the lymphocytes 77 per cent; hemoglobin 75 per cent; red cell count 3,770,000, the swelling of the lymph nodes diminished. After treatment had been discontinued the patient's general condition and blood picture remained more or less unchanged until June 1943, when he began to suffer from increasing difficulty in swallowing, and in August of the same year a plum-sized saccular diverticulum was demonstrated in the esophagus, at the level of the clavicle. The blood counts in August 1943 were: leukocytes 11,000, with 94 per cent lymphocytes; hemoglobin 81 per cent; red cells 3,540,000. At the same time, the swelling of the lymph nodes had increased somewhat. Roentgen irradiation was given to the nodes in the neck, and was repeated in December, with a resultant reduction in the leukocytes to 8,000 per cu.mm. with lymphocytes 77 per cent. In 1944, swallowing became more difficult, but the lymph nodes got smaller. (May, 1944, leukocytes 3,400, with lymphocytes 65 per cent; in November, same year, leukocytes 4,700, with lymphocytes 45 per cent.) In February 1945, the patient was operated on in another hospital for the diverticulum of the esophagus, and the swallowing difficulty disappeared entirely. Later in the same year there again occurred swelling of the lymph nodes, and roentgen treatment was again applied with good effect. (August 1945: hemoglobin 74 per cent, red cells 3,310,000, white cells 1,400, with 37 per cent of lymphocytes.) In October, same year, he was admitted to another hospital suffering from enteritis, and in the following two years he was repeatedly treated.
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for persistent diarrhea, but steadily became more feeble. The treatment was chiefly dietetic, and radiation treatment was not given. The leukocyte count remained low: in October 1945, for instance, 1,160 per cu.mm., with lymphocytes 74 per cent; in August 1947 4,500, with lymphocytes 24 per cent. The sternal marrow was heavily infiltrated with lymphocytes. In September 1947 he died. Only partial necropsy was performed. A firm, annular infiltration extending a little above and below the pylorus was found in the stomach. Its surface was somewhat ulcerated. There were numerous lymph nodes in the mesentery. The liver was not enlarged and the spleen weighed 315 Gm. Histologic examination revealed an adenocarcinoma in the pyloric region. There were histologic changes in the spleen, liver, mesenteric lymph nodes and colon consistent with lymphatic leukemia. In the liver only very slight periportal infiltrations were noted. There were no metastases in the organs examined.

Comment: In this case a typical lymphatic leukemia with characteristic blood picture was demonstrated in 1941. The anamnestic data make it probable that the condition had already existed for a number of years. From 1941 until the patient’s death in 1947 the leukemia had, in spite of very moderate radiation treatment, remained aleukemic. In the last two years, there had been gastric and intestinal symptoms and increasing cachexia, and at the necropsy an ulcerated adenocarcinoma was found in the region of the pylorus, but lymphatic infiltrations in the lymph nodes, liver, spleen and colon were present. No other organs were examined.

Though the rather protracted aleukemic phase after a definite leukemic beginning is unusual, there can hardly be any doubt that the patient had a genuine leukemia. The long duration of the leukemic symptoms makes it overwhelmingly probable that the cancer of the stomach was a disease of later origin.

Besides this case, we have had occasion to observe 2 cases of cancer of the stomach, in which the first diagnosis both clinically and hematologically was chronic lymphatic leukemia, but in which the leukemic symptoms disappeared little by little as the cancer of the stomach developed. The first of these has already been published, and shall therefore only be briefly recapitulated here.

P. I. P. (Radium Center 1114/35), farmer, born 1879. In 1935, there appeared a plum-sized swelling of lymph nodes in his axillae and groins, and at the same time he began to suffer from increasing fatigue. The lymph node swelling was constant for four months, and he was admitted to the Radium Center. There was no enlargement of the liver or spleen, but roentgen examination of the lungs showed enlarged hilus glands. (For the blood findings, see the condensed table 1.) Most of the lymphocytes were small, rich in chromatin, but with very sparse cytoplasm. A few were atypical, with lobulated or bi-nucleated nuclei. There were a number of disintegrated cells. A brief series of spray x-radiations, were given, seemingly with good effect. The man remained perfectly well until the fall of 1937, when dyspeptic symptoms began to develop. In another hospital, exploratory laparotomy was performed and a large, inoperable carcinoma of the stomach, invading the liver was found. In January 1938, he was readmitted to the Radium Center, to be treated with roentgen-ray for the tumor of the stomach. It was treated locally. At that time there was no swelling of the peripheral lymph nodes and no enlargement of the spleen. He died November 1938. Necropsy showed a large carcinoma of the stomach, with invasion of the left lobe of the liver and metastases to small glands along the lesser curvature, but otherwise no metastases were found. There were no other glandular swellings, and the spleen was not enlarged. Histologically, the tumor of the stomach was a typical adenocarcinoma. There were no signs of lymphatic leukemia in the liver, spleen or kidneys. In the bone marrow there were a few very small groups of small lymphocytes, but otherwise normal erythromyelopoiesis.

Comment: The results of some of the blood examinations are shown in Table 1; further details may be found elsewhere. It will be seen that when the patient was admitted in 1935, the blood picture showed a marked lymphatic reaction and the
lymphocytes showed morphologic abnormalities such as are often seen in lymphatic leukemia. In the course of a few months, the total leukocyte count dropped to normal values and at the same time the proportion of lymphocytes decreased, until at the time of the patient's death, there was a marked relative and absolute lymphopenia. In this case, it is difficult to say when the tumor in the stomach began to develop. When laparotomy was performed in 1938, he had been ill for about two years, and at the time of that operation the tumor was already very large and inoperable. It is therefore quite possible that the leukemoid state and the neoplastic growth may have developed simultaneously.

The following case in many respects shows a similar development. Unfortunately there is no microscopic examination of the gastric tumor available, but it is reasonable to suppose that the patient had a non-leukemic malignant growth there.

E. J. (Radium Center 1330/47), electrician, born 1871. Past history without interest. For six months had pains in the epigastrium after meals, and occasional vomiting. In May 1947, referred to the Radium Center to be treated for carcinoma of the stomach. He had lost 3-4 Kg. in weight during the preceding six months. There had been no angina or fever in connection with his present illness. The patient was pale and emaciated. Numerous moderate enlargements of lymph nodes were present in the neck, axillae and groins, but no palpable enlargement of liver or spleen. In the epigastrium an irregular tumor was felt, whose size was difficult to determine. There was no free acid in the stomach. Roentgen examination of the stomach showed a notched, irregular, eroded mass with a filling-defect, for a distance of 8 or 9 cm. on the greater curvature. This was the size of an orange and extended into the lumen. On admission the sedimentation rate was 43 mm./hour, hemoglobin 77 per cent, red cells 3,680,000, white cells 11,600 with neutrophils 77, eosinophils 0 and mononuclears 83 per cent. Most of the mononuclears were of the small lymphocyte type with very scant cytoplasm and a nucleus rich in chromatin. But a few larger forms were also present with a monocytoid configuration and structure, often with distinct nucleoli. A number of “smudge” cells were seen. Only a few typical monocytes were present. No McKinley cells. The sternal marrow was rich in cells and contained over 80 per cent of these atypical, mononuclear cells. Microscopic examination of a lymph node puncture showed typical lymphatic leukemic changes. The Paul-Bunnel test was negative. The patient was treated with x-rays over the tumor of the stomach (rotatory irradiation): 160 Kv., 94 ma., through 0.5 mm. Cu. + 1 mm. Al., half-layer value 0.7, distance 50 cm.; two
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series, each of 2,700 r. The treatment did not reduce the size of the epigastric tumor substantially, and the roentgenographs showed only moderate regression of the tumor in the stomach. The patient was controlled as an out patient, but became feebler and lost weight. The leukemic blood picture disappeared. (June 2, 3,500 white cells, 46 mononuclears; June 17, 4,800 white cells, 16 mononuclears and no atypical cells. The mononuclear cells could now easily be divided in 9 per cent typical monocytes and 7 per cent lymphocytes.) In June 1947, the sternal marrow showed almost normal conditions, with only 14 per cent lymphocytes in the smears. The swelling of the lymph nodes also gradually diminished, and by August of the same year, they were only of hazelnut size. During the following months, the patient was readmitted for renewed treatment. The lymph nodes had become still smaller, but the tumor of the stomach had become larger. The blood counts were as follows: hemoglobin 45 per cent, red cells 2,100,000, white cells 6,400, platelets 4,000. Neutrophils 83,5, eosinophils 0, lymphocytes 1,5, monocytes 6. No atypical cells. He was again given roentgen treatment, this time to two fields, each of 10 x 10 cm., over the epigastrium: 160 Kt., 4 ma. through 1 mm. Cu + 1 mm. Al, distance 40 cm.; 600 r, in all, to each field. At the time of discharge there was no glandular swellings except a single bean-sized node on one side of the groin. The blood counts at this time (October 10) were: hemoglobin 62, red cells 3,230,000, white cells 3,400; neutrophils 88, lymphocytes 10, monocytes 6. As will be seen, there was now both relative and absolute lymphopenia. The sternal marrow showed no evidence of leukemia. Three weeks later he died at home, and unfortunately we did not succeed in obtaining a necropsy.

Comment: This third case has some resemblance to the foregoing. On admission, there were clinical and hematologic signs of lymphatic leukemia with typical changes in the sternal marrow and the examined lymph node. At the same time, a tumor was found in the stomach, and as this grew larger all signs of leukosis disappeared, the swellings of the lymph nodes subsided, the sternal marrow became normal and at last there was marked lymphopenia in the blood. Unfortunately we were unable to examine the tumor of the stomach histologically, but it is hardly possible that it could have been a lymphatic leukemic growth, as these are extremely radiosensitive, while in this case there was very moderate regression in spite of intensive local irradiation with roentgen rays.

The coexistence of cancer and leukemia in the same individual has been observed rather often, and some of the reported cases of this association have recently been reviewed by Videbaek. In the present study, it is specially the combination of cancer and lymphatic leukemia which is of interest. Such cases have been reported by Lannois and Regaud (cancer of the uterine cervix), Marischler (hypernephroma), Fuhsi (cancer of the skin), Genévrier (pulmonary cancer), Scheuller (cancer of the skin), Brückner (cancer of the uterine cervix) Schreiner and Wehr (cancer of the skin, 2 cases; pulmonary cancer, 1 case; mammary cancer, 1 case), Saupe (cancer of the stomach), Denoyer (cancer of the larynx), Pulvertaft (cancer of the skin), Penzold (cancer of the stomach), Askanazy (cancer of the esophagus), Dustin (cancer of the stomach), Engelbreth-Holm (cancer of the lip, 1 case; cancer of the skin, 5 cases; cancer of the penis, 1 case), Hotz (cancer of the kidney), Švejda (cancer of the stomach, 1 case, cancer of the larynx, 1 case) Gertler (cancer of the skin), Ovnbøl and Therkildsen (cancer of the breast and the prostate in the same individual), Delcourt (mammary cancer, 7 cancer of the bile ducts in the liver), Morrison (cancer of the pancreas), Berk and Movitt.

* One must consider the possible effect on the leukemia of the local roentgen ray therapy directed to the stomach. Editor.
(cancer of the larynx), Videbaek\textsuperscript{4} (cancer of the skin). In this review, we have omitted the combination of tumors originating in the hemopoietic tissue (lymphosarcomas, reticulosarcomas, myelomas, etc.) with leukemic blood pictures.

Petri\textsuperscript{23} found carcinoids in the intestines of 2 patients with aleukemic lymphatic leukemia and called attention to the advisability of a close examination of the intestine of patients with leukemia, with the view of the possible presence of such tumors, which are often small and difficult to distinguish from Peyer's patches, especially if there is also leukemic infiltration in the gut.

That leukemic reactions of the myeloid type may occur in connection with malignant tumors is well known, though the mechanism of their development is not quite clear. Lymphatic reactions, on the other hand, are rarely seen in connection with malignant tumors (here we again omit the special tumors arising from the hemopoietic tissue). Reich\textsuperscript{25} described a curious case of an adenocarcinoma of the sigmoid in a man 55 years old with 18,700 leukocytes per cu.mm., 91 per cent of which were lymphocytes. The sternal marrow showed marked infiltration of lymphocytes, many of which were abnormal. The day before he died, the leukocyte count rose to 103,000 per cmm., with 95 per cent lymphocytes, but at necropsy there was no leukemia. Reich suggests that the unusual hematologic picture may have been due to an action of the carcinoma on the hemapoietic tissue. The necropsy revealed generalized metastases, including the bone marrow. Müller and Werthemann\textsuperscript{20} mention a case of lymphocytosis associated with mammary cancer with metastases to spleen, lymph nodes and bone marrow. There were 33,000 leukocytes per cmm., with 65 per cent lymphocytes. At necropsy, no leukemic changes were found in the organs. A case which is not quite clear, however, is reported from Russia, by Šal.\textsuperscript{27} The patient was a man, 55 years old, with 434,000 leukocytes per cu.mm., 99 per cent of which were lymphocytes. At necropsy, cancer of the peritoneum (? primary tumor) was found, with enlargement of the spleen and liver, but no enlargement of the lymph nodes. The bone marrow was normal. In the case of a woman 29 years old, reported by Winans,\textsuperscript{28} blood examinations showed up to 18,500 leukocytes per cu.mm. with 85 per cent lymphocytes, but there was no enlargement either of the spleen or the lymph nodes. Some time afterwards, she experienced pains in the lower part of the abdomen, and at the operation a pseudomucinoid cyst was removed from the right ovary, and a papillary adenoma from the left. The lymphocytosis disappeared, but had already decreased before the operation and seemed to have been due to a febrile infection of the upper air passages and not to the tumors. Rohr and Hegglin,\textsuperscript{24} in their monograph on the occurrence of tumor cells in sternal punctures, briefly mention a case of a simple, solid carcinoma of the cardia in a man, 75 years old, with 25,000 leukocytes per cu.mm., 34 per cent of which were lymphocytes. "Die Lymphocyten sind vorwiegend jung (Bild der lymphatischen Reaktion)." In the sternal marrow, there were 17.6 per cent lymphocytes besides the tumor cells. In Silberstern and Pechterewa's case\textsuperscript{31} of a cancer of the rectum in a 72-year old male there were 18,000 leukocytes with 85.5 per cent lymphocytes, without other signs of leukemia. The autopsy revealed metastases to the regional lymph nodes but no leukemic involvement of the organs and only slight lymphocytic infiltration of the liver and bone marrow.
In comparison with the myeloid reactions in malignant tumors, lymphatic reactions are extremely rare. Moreover, they seem to be different from the myeloid in several respects; thus they, in contrast to these, which as a rule are a late phenomenon, often occur at a very early stage of the development of the cancer, sometimes even at the same time as the latter. The mechanism which elicits the lymphatic reactions in these cases is quite obscure. Silhol thought that metastases from cancer of the stomach to regional lymph nodes might give rise to lymphocytosis, but the early occurrence of the lymphatic reactions makes it doubtful if metastases to lymph nodes play any part. Another strange thing about these reactions is, as far as one can conclude from a rather few cases, their tendency to become less pronounced as the malignant tumor grows larger. The same tendency can be noticed as regards the lymphatic leukemias associated with cancer; for instance, in Marischler's case of hypernephroma combined with chronic lymphatic leukemia, and in the first of the cases reported in the present communication. In Marischler's case, the number of lymphocytes steadily decreased, and the lymph nodes gradually became smaller as the disease developed. He supposed that this was due to an effect of cancer 'toxins' on the leukemic process, similar to the well-known effect of certain infections. It must be remembered, however, that the lymphatic tissue is apt to be strongly affected by cachexia and inanition, conditions which appear with malignant tumors, especially when these have their origin in the gastrointestinal tract.

Even in the uncomplicated cases of chronic lymphatic leukemia there is often a fall in the lymphocyte content of the blood during the last days of life, and the spleen and lymph nodes may become smaller, even without therapy, though, of course, this does not mean that there is an entire disappearance of the leukemic changes in the organs. Of course it is a question if certain malignant tumors of the gastrointestinal tract do not have a repressing effect on the leukemic processes in the organs. That tumors of the stomach do not always have this effect, is clearly seen from Penzold's case, in which the neoplastic growth and the leukemic processes existed side by side and were even believed by Penzold to have activated each other. It is clear that as basis for judgment respecting the reciprocal effect of the tumor and the leukemia only those cases can be used in which the observation time has been sufficiently long, and in which the patient died either of the leukemia or of the malignant tumor, and not of some irrelevant disease. In Dustin's case, for instance, of stomach cancer with lymphatic leukemia, the patient was only observed a few days and died of an intercurrent infection.

**Summary**

The author reports the case of a patient with chronic lymphatic leukemia, who after some years developed dyspeptic symptoms, increasing cachexia, and eventually died. The leukemia had been subleukemic for several years. Necropsy revealed an adenocarcinoma of the pylorus and lymphatic leukemic changes in the lymph nodes, spleen and liver. In two other cases a lymphatic leukemic blood picture and clinical signs of leukemia (including lymph node enlargements and leukemic changes in the bone marrow) gradually disappeared as tumors of the stomach de-
veloped, and in both cases the leukemic blood picture was replaced by a state of lymphopenia. In one of them, the necropsy revealed an adenocarcinoma of the pylorus; in the other, necropsy could not be obtained, but the clinical picture and the radioscopic examinations strongly suggested carcinoma of the stomach in this case, too. These last two cases must be interpreted as lymphatic leukemoid states produced by the presence of the carcinomatous neoplasms, though the possibility cannot be excluded that certain carcinomas of the gastrointestinal tract may be capable of primarily or secondarily exercising an inhibitory influence on the leukemic processes.

In connection with the report of these cases, the author reviews the cases from the literature, of lymphatic reactions in cancer and of the coexistence of lymphatic leukemia and cancer in the same individual.

REFERENCES

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