Extensive Leukemic Infiltration of the Gastrointestinal Tract during Apparent Remission in Acute Leukemia

By Charles R. Everett, Mary Ellen Haggard and William C. Levin

Generally, there is good correlation between hematologic manifestations of acute leukemia and clinical and/or histologic evidence of parenchymal infiltration by leukemic cells. There has been encountered a number of reports of the association of central nervous system infiltration with acute leukemia "in remission". Invariably, such remissions have been previously induced by treatment with one of the antimetabolites. This has suggested the possibility that the natural history of the disease has been significantly altered by exposure to these therapeutic agents.

The patient herein reported was unique in that extensive leukemic infiltration of the gastrointestinal tract, severe enough to be responsible for her death, existed despite the fact that there was no ante-mortem clinical or hematologic evidence of relapse of the previously diagnosed acute leukemia. No previous report of such an observation has been found.

Case Report (UH #98651-M)

First admission. The patient, a 7 year old white female, entered John Sealy Hospital on April 15, 1960, with a 3-month history of a chronic upper respiratory infection which had responded poorly to antibiotic therapy. The patient had been transfused with one unit of blood 1 week before entry. Examination on admission revealed fever, generalized shotty adenopathy, and hepatosplenomegaly.

Laboratory studies revealed: RBC 4.26 million per cu. mm., hemoglobin 11.8 Gm. per cent, reticulocytes 1.0 per cent, WBC 17,000 per cu. mm. with 7 per cent polymorphonuclear leukocytes, 7 per cent stabs, 5 per cent metamyelocytes, 1 per cent myelocytes, 2 per cent eosinophils, 68 per cent mature lymphocytes, 7 per cent early lymphocytes, 1 per cent lymphoblasts, 2 per cent monocytes, platelets 79,280 per cu. mm. Examination of the bone marrow showed a picture characteristic of acute lymphoblastic leukemia (fig. 1).

The initial therapy consisted of 6-mercaptopurine, 50 mg. daily, and prednisone, 50 mg. daily. A prompt remission ensued. At the time of discharge, 36 days later, the white blood count was 4200 per cu. mm. No lymphoblasts were seen. The hemoglobin was 9.5 Gm. per cent with a reticulocytosis of 8.0 per cent. Examination of the marrow revealed normal myeloid and erythroid elements and megakaryocytes. Only an occasional lymphoblast was present. There was no hepatosplenomegaly, and the patient was clinically asymptomatic.

She was discharged from the hospital on 6-mercaptopurine only.

Second admission. The patient was readmitted on April 5, 1961, for treatment of a relapse. The major symptom was lethargy during the previous 3 weeks. For the preceding year, treatment had consisted of 6-mercaptopurine in daily doses of 25 to 50 mg. On physical examination the temperature was 101 F. and hepatosplenomegaly and ecchymotic areas on all extremities were present.

Laboratory data: WBC 1850 per cu. mm. with 14 per cent granulocytes, 14 per cent lymphoblasts, and 72 per cent lymphocytes. Hemoglobin was 6.6 Gm. per cent and the
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Fig. 1.—Photomicrograph of bone marrow on April 24, 1960 showing almost complete replacement by leukemic lymphoblasts.

platelet count was 18,000 per cu. mm. The bone marrow was consistent with a relapse in the leukemia similar to the picture initially described (fig. 1).

The 6-mercaptopurine was discontinued and the patient was placed on a regimen consisting of prednisone 40 mg. daily, Methotrexate 2.5 mg. daily, and blood transfusions. When the patient was discharged 56 days later, the WBC was 4350 per cu. mm. with 60 per cent granulocytes, 33 per cent lymphocytes, and 7 per cent monocytes. The hemoglobin was 10.7 Gm. per cent, reticulocytes 4.6 per cent, and the platelets 434,000 per cu. mm. The ecchymoses and hepatosplenomegaly no longer were present. The clinical improvement and the return of the peripheral blood values to near normal levels were interpreted to indicate a second remission. Prednisone was discontinued and the patient was discharged on Methotrexate 2.5 mg. daily.

Final admission. After the second admission the patient exhibited fatigue and poor appetite. The dose of Methotrexate had been unchanged. Daily fever was present for 3 weeks prior to admission. Beginning 1 week before this hospitalization, almost daily episodes of intermittent colicky left abdominal pain, without change in bowel function, were noted. She was readmitted on August 2, 1961.

She was pale and thin and demonstrated cushingoid facies. The temperature was 104 F. orally and the pulse 106 per minute. There was no hepatosplenomegaly. The abdomen was slightly distended and tender to the left of the umbilicus. The bowel sounds were normal.
Laboratory data: hemoglobin 11.8 Gm. per cent, reticulocytes 1.2 per cent, WBC 6,700 per cu. mm., mature granulocytes 43 per cent, stabs 7 per cent, metamyelocytes 2 per cent, lymphocytes 44 per cent, monocytes 4 per cent, platelets 284,200 per cu. mm. On August 3, 1961, the marrow aspirate revealed normal cellularity. Myeloid elements were normal. The erythroid series was quantitatively normal and megakaryocytes were not reduced. Only occasional lymphoblast was seen (fig. 2).

Hospital course: Methotrexate was continued and prednisone, 20 mg. per day, was added. Several days after admission, progressive nausea and painful abdominal distention developed. Terminally, there were several episodes of bloody diarrhea, and the free abdominal fluid was confirmed by paracentesis. Daily temperature elevations to 105 F. occurred despite antibiotics, and the patient expired on the 10th hospital day.

The complete hematologic course is graphically presented in figure 3. Post-mortem examination revealed ulceration of multiple leukemic infiltrates in the gastrointestinal tract with perforation at four sites in the upper jejunum. Microscopic examination showed these infiltrates to consist of masses of lymphoblasts invading all layers of the intestinal wall producing marked degenerative changes in the muscularis (fig. 4). Ulcerations occurred only in sites of leukemic infiltration. Leukemic infiltrates also were present in the lungs, liver, and spleen (weight 280 Gm.). There was marked adenopathy of the mediastinal, hilar, periaortic, and mesenteric nodes, most striking in the latter with masses up to 6 cm.
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Fig. 3.—Summary of hematologic course and major therapy during the course of observation.

in diameter. No peripheral adenopathy was present. Massive hemorrhage into the gastrointestinal tract and peritoneal cavity had occurred.

DISCUSSION

The incidence of leukemic infiltration of the gastrointestinal tract is variable, although the occurrence of gastrointestinal infiltrates is almost invariably noted in the presence of “active” disease or leukemia in relapse. Kirschbaum and Preuss reported gastrointestinal involvement in 13 per cent of 123 leukemic patients who were studied at autopsy. Maher cited the incidence of gastrointestinal involvement as 23 to 62 per cent for all types of leukemias; and, contrary to other investigators, stated that the incidence of infiltration in myelocytic leukemia is almost as high as in lymphocytic leukemia. A series of 76 necropsies performed on leukemic patients with 48 instances (63 per cent) of gastrointestinal involvement was reported from Japan.

Infiltration with leukemic cells may occur from the cardia to the anorectal area, the stomach being the most common site. The esophagus is almost never involved. Pearson, Stasney and Pizzolato have noted a distinctive feature of lymphocytic leukemia in that involvement occurs only in the mucosa and submucosa with sharp demarcation of the process from the muscularis. This is not true for the myelocytic variety. The infiltrate may be restricted to lymphoid follicles, to lymphoid tissue, to Peyer's patches, or the involvement may be diffuse. Frequently, the infiltrates form plaques and nodules, or even large polypoid masses, most commonly in the stomach and colon. The gastric lesions may be diffuse, forming large cord-like rugae. They may become so massive as to be radiologically indistinguishable from carcinoma. Intussusception as well as intestinal obstruction may occur.
as a result thereof. Ulceration of the leukemic infiltrates, even with perforation, has been reported. Rectal lesions may be manifested as polyp-like growths, abscesses, or fistulae.

Usually, the leukemic patient with gastrointestinal infiltration has no gastrointestinal symptomatology, even in the presence of extensive involvement. The commoner symptoms are quite vague and non-specific, e.g., nausea, mild abdominal pain, or diarrhea. One of the most frequent symptoms is gastrointestinal bleeding. Rathbun reported leukemic infiltration responsible for 17 of 89 cases of rectal bleeding in infants and children. Melena as an initial symptom is not unusual, and, in one instance, subtotal colectomy was required to control bleeding from diffuse leukemic infiltration and ulceration of the colon. Gastroduodenal ulceration with hemorrhage may be a presenting symptom. This can be due to ulceration of necrotic leukemic infiltrates, or secondary to benign peptic ulcer, the incidence of which is increased in leukemia. In one report of massive upper gastrointestinal bleeding occurring in five leukemic patients, only one was shown to have bled from a leukemic infiltrate. Hemorrhage from the intestinal tract in leukemia is

Fig. 4.—High power view of a section of jejunum revealing infiltration of the bowel mucosa by lymphoblasts. This involved all layers of the jejunum.
more common in the acute forms and is thought to be due to an associated thrombocytopenia.\textsuperscript{3,20} Because of the paucity of gastrointestinal symptoms associated even with massive gastrointestinal lesions in leukemia patients, the appearance of such clinical manifestation requires a thorough search for all other possible types of gastrointestinal disease. All cases with gastrointestinal tract involvement collected from a careful search of the literature were described as having evidence of leukemia in relapse as reflected by changes in the peripheral blood and/or bone marrow.\textsuperscript{7,14,16,18,19,21-29}

The term remission is used to describe an asymptomatic period in the course of acute leukemia. It is not intended to suggest complete absence of disease. Therefore, apparent clinical and hematologic normalcy may, at any time, be interrupted by manifestations of disease resulting from parenchymal infiltration, even though the peripheral blood and marrow do not reflect the development of a "relapse." Heretofore, the occurrence of central nervous system involvement in this situation has been attributed to the existence of the blood-brain barrier, which is purported to prevent ingress of the antimetabolite into the central nervous system.\textsuperscript{1,20} This explanation obviously does not apply to the phenomenon exhibited by the patient described above.

**SUMMARY**

A child with acute leukemia in an apparent hematologic remission who succumbed to the complications arising from extensive leukemic infiltration of the gastrointestinal tract is reported.

This cannot be explained by any unique anatomical properties of the circulation, such as have been proposed for central nervous system infiltration under similar circumstances.

**SUMMARIO IN INTERLINGUA**

Es reportate le caso de un juvene con acute leucemia in un apparente remission hematologic qui succumbeva al complicationes resultante del extense infiltration leucemic del vias gastrointestinal.

Isto non pote esser explicate per particular proprietates anatomic del circulation del typo que ha esite proponite pro explicar infiltration del sistema nervose central sub simile circumstantias.

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